EXPLORING ASSOCIATIONS BETWEEN ENVIRONMENTAL RISK FACTORS AND LOW BIRTH WEIGHT USING GEOGRAPHIC BIG DATA

by

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TABLE OF CONTENTS

Page

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

ABSTRACT

Low birth weight (LBW) is defined as newborns who are born weighing less than 2,500 grams. LBW is not only one of the adverse pregnancy outcomes, but also an important predictor of infants' health. LBW is associated with many risk factors, among which environmental risk factors account for an important portion. This dissertation examines the association between maternal residential exposure to environmental risk factors and LBW in offspring, focusing on ambient air pollution and ionizing radiation near nuclear facilities.

Although a growing body of literature has studied environmental risk factors and their relationships with LBW, especially during the last decade, there are some limitations in these reported studies. First, the impact of a significant number of air pollutants on LBW has not been investigated. Second, most studies have used predefined exposure windows (e.g. entire pregnancy, trimesters, and months), which restricted the discovery of more critical exposure windows with more flexible time durations and starting times. Third, few studies have taken into account exposure windows before conception. Fourth, there has been little research about the influence of ionizing radiation near nuclear facilities on LBW. This dissertation fills these gaps in the literature through examinations of (1) association between maternal residential exposure to chemicals released into the air from Toxic Release Inventory (TRI) facilities and LBW in offspring in Texas, (2) association between maternal residential exposure to chemicals monitored

by the Texas Commission on Environmental Quality (TCEQ) air quality monitors and LBW in offspring in Texas, and (3) association between maternal residential proximity to nuclear facilities and LBW in offspring in Texas. I call them the TRI Chemicals-LBW association study, the TCEQ Chemicals-LBW association study, and the Nuclear Facilities-LBW association study, respectively.

All three studies used case-control study designs. The birth data used in the three studies were birth certificates for all registered births in Texas from 1996 to 2008 obtained from the Center for Health Statistics in the Texas Department of State Health Services (TX DSHS).

The TRI Chemicals-LBW association study collected air emission data in Texas during 1996-2008 from the United States Environmental Protection Agency TRI program and air quality monitoring data in Texas during 1996-2008 from the TCEQ Texas Air Monitoring Information System (TAMIS) database. This study estimated maternal residential exposure to TRI chemicals using a modified version of Emission Weighted Proximity Model (EWPM). The model parameters for different TRI chemicals were calibrated through a geocomputational method. Binary logistic regression was used to generate odds ratios for the TRI Chemical-LBW associations. The odds ratios were adjusted for birth year, public health region of maternal residence, child's sex, gestational weeks, maternal age, education, and race/ethnicity. Based on these adjusted odds ratios, this study identified ten chemicals that were most likely to be associated with LBW from

the 449 TRI chemicals. These ten chemicals are styrene, n-hexane, benzene, cumene, methyl isobutyl ketone, cyclohexane, zinc (fume or dust), o-xylene, propylene, and ethylene. In this case-control study, case-mothers were more likely to have a higher level of exposure to these ten chemicals than control-mothers. For four of the ten chemicals (styrene, o-xylene, n-hexane, and benzene), LBW risks increased monotonically when the estimated exposure intensities increased.

The TCEQ Chemicals-LBW association study collected air quality monitoring data in Texas during 1996-2008 from the TCEQ TAMIS database. This study estimated maternal residential exposure to TCEQ chemicals in different exposure windows using a spatio-temporal method that took into account residential distance to air quality monitors and ambient concentrations of chemicals within exposure windows. For each combination of the 367 TCEQ chemicals and various exposure windows, this study utilized binary logistic regression to generate odds ratios for the TCEQ Chemical-LBW associations. Based on these odds ratios, this study identified the top ten chemicals (benzaldehyde, 4-methyl-1-pentene, hexanaldehyde, sum of PAMS target compound, m-tolualdehyde, n-undecane, p-tolualdehyde, ethylene dibromide, n-butane, and trans-crotonaldehyde) and corresponding critical exposure windows that showed strongest impact on LBW in offspring. Findings from the study suggested that case-mothers were more likely to be exposed to higher intensities of these ten chemicals within the critical exposure windows than control-mothers. The critical exposure windows identified in the

study had flexible time durations (e.g. 30 days, 90 days) and starting time (e.g. before conception and after conception). Most of the critical exposure windows after conception found in this study were located within the second or third trimester of pregnancy. Critical exposure windows before conception were also identified in eight of the ten TCEQ chemicals, which indicated that mothers who were prepared for pregnancy should pay close attention to the air quality in their living environment before conception. Methodologically, the study proposed a standardized protocol for interactively exploring critical exposure windows of air pollution-LBW associations based on the analysis of massive georeferenced air quality monitoring data.

The Nuclear Facilities-LBW association study obtained data from United States Nuclear Regulatory Commission for nuclear facilities in operation during 1996-2008 in Texas. This study categorized the LBW case/control births into multiple proximity groups based on distances between their maternal residence and nuclear facilities. Then, this study used a binary logistic regression model to examine the association between maternal residential proximity to nuclear facilities and low birth weight in offspring. The odds ratios were adjusted for birth year, public health region of residence, child's sex, gestational weeks, maternal age, education, and race/ethnicity. In addition, this study conducted sensitivity analyses using different distance thresholds. Compared with the reference group (>50 km), the exposed groups did not show a statistically significant increase in LBW risk (adjusted odds ratio (aOR) 0.91, (95% confidence interval (CI)

0.81, 1.03) for group 40-50 km; aOR 0.98 (CI 0.84, 1.13) for group 30-40 km; aOR 0.95 (CI 0.79, 1.15) for group 20-30 km; aOR 0.86 (CI 0.70, 1.04) for group 10-20 km; and aOR 0.98 (CI 0.59, 1.61) for group 0-10 km). These results were also confirmed by results of the sensitivity analyses. The results suggest that maternal residential proximity to nuclear facilities is not a significant factor for LBW in offspring.

1. INTRODUCTION

1.1. Background

Humans and the environment are never independent, because there are dynamic and complex interactions between them (Knox and Marston 2012). Human activities can impose positive or negative influence on the environment; in return, the environment can also have an effect on people's life in either a positive or a negative way. Human environmental science research focuses on the interactions of humans and the environment. It aims at improving the quality of life for individuals, families, and communities in the environment.

Human reproduction is one of the most important aspects of human life. It has a significant influence on the quality of life for both parents and newborns. In the United States, around six million pregnancies occur each year (U.S. CDC 2015). However, not all women have a safe term pregnancy and deliver a healthy infant (U.S. CDC 2014).

Birth weight is the weight of a newborn measured immediately after birth (U.S. CDC 2012). Low birth weight (LBW) is defined as newborns with birth weights of less than 2,500 grams (or 5.5 pounds) (WHO 1992). LBW infants may have higher risks of many health problems than infants born with normal weight (U.S. CDC 2012). The health problems not only include infant mortality and/or morbidity (Reynolds et al. 2004; McCormick 1985), but also involve adverse health outcomes in later life, such as coronary heart disease, hypertension and type II diabetes (Osmond and Barker 2000), stroke (Lawlor et al. 2005), delayed motor and social development or learning disabilities

(U.S. CDC 2012), and other adult chronic diseases (Joseph and Kramer 1996). Therefore, LBW has become an important predictor of infants' health (Ebisu, Belanger, and Bell 2008).

Figure 1.1 shows the percentage of low birth weight live term singleton births in the 48 continental United States during 2000-2010. This rate is restricted to singleton term births, because gestational age and plurality of birth are directly related to the birth weight of an infant. This rate varies between 1.3% and 4.8% in different states in the U.S. The pattern was similar across all eleven years. Louisiana, Mississippi, Alabama, and Wyoming always had the highest rates (3.2% - 4.8%); while Oregon, North Dakota, Minnesota, and Iowa always had the lowest rates (1.3% - 2.1%). Texas, which is the study area of this dissertation, has a yearly LBW rate of 2.5% to 3.0% during 2000-2010, accounting for 7,906-10,363 LBW infants per year.

As shown in Figure 1.2, LBW is associated with many risk factors, including genetics, maternal characteristics and behaviors (e.g. younger than 15 years and older than 35 years, smoking, and drinking alcohol), socioeconomic factors (e.g. low income, low educational level, stress, domestic violence, and unmarried), and exposure to environmental risk factors (Valero De Bernabé et al. 2004; U.S. CDC 2012). This dissertation focused on investigating the relationship between environmental risk factors and low birth weight.

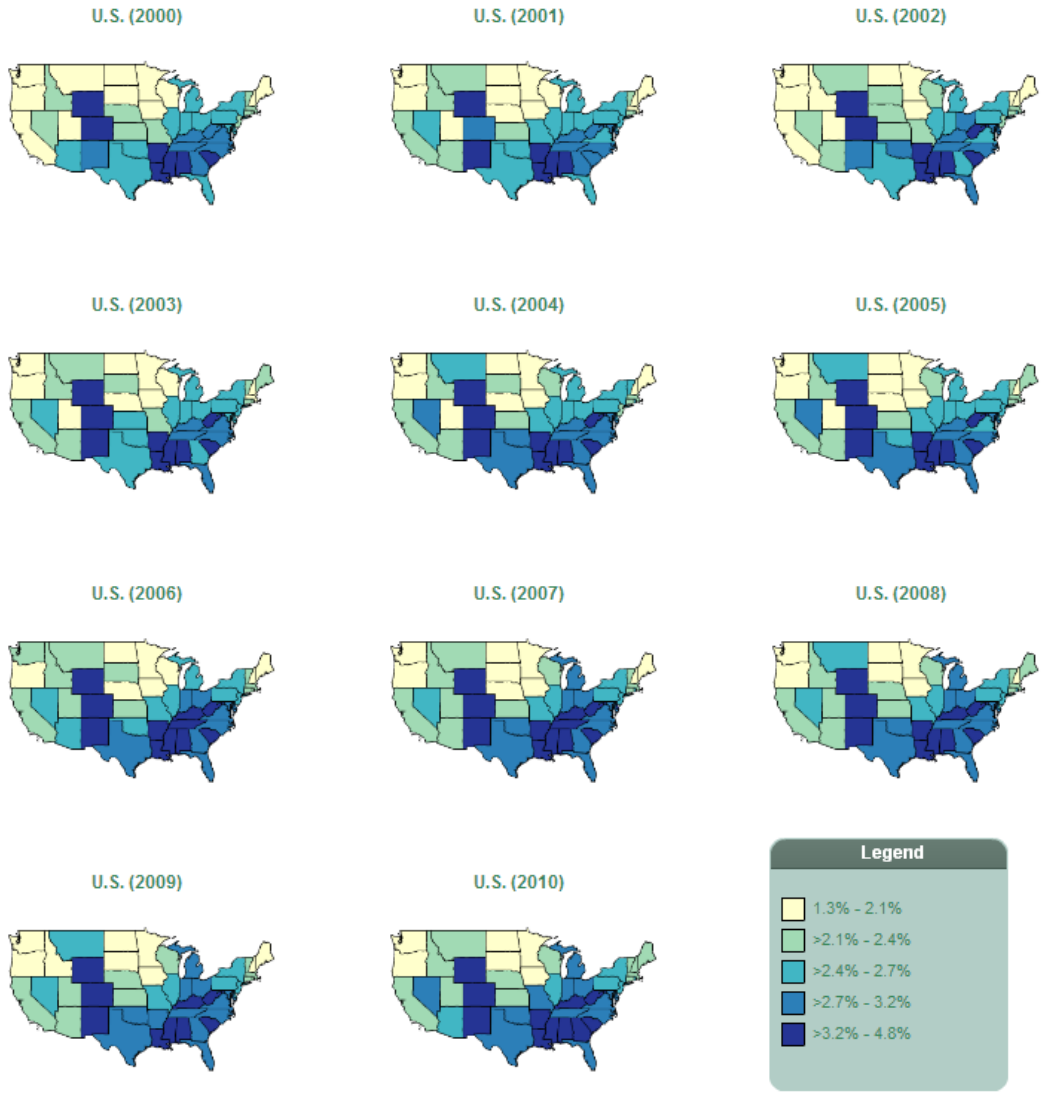

Figure 1.1 Percentage of low birth weight live term singleton births in the 48 continental United States during 2000-2010 (modified from U.S. CDC 2014)

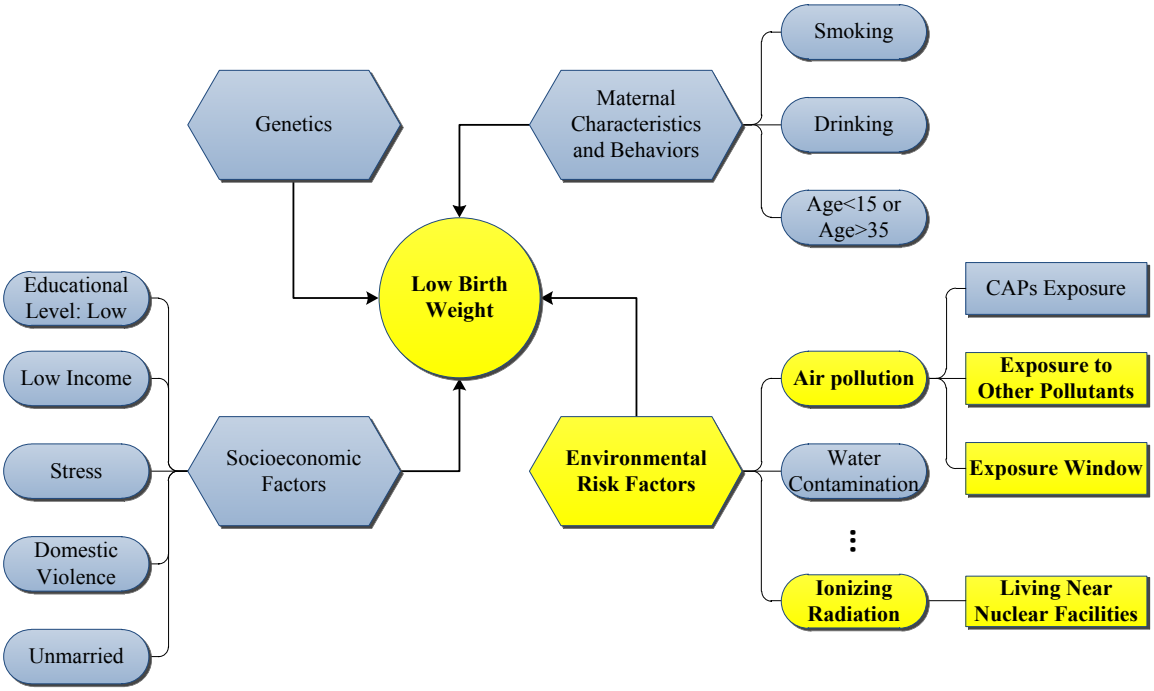

Figure 1.2 Risk factors for LBW (modified from U.S. CDC 2012).
(Items marked in yellow are the research topics of this dissertation.)

Potential environmental risk factors include almost everything surrounding an individual on daily basis, such as air pollution, water contamination, ionizing radiation, lack of surrounding greenness, among other conditions. Air pollution and its association with LBW have been reported in many studies. The results have been summarized in several reviews (Glinianaia et al. 2004; Maisonet et al. 2004; Ritz and Wilhelm 2008; Srám et al. 2005). The influences of public drinking water contamination on LBW have also been investigated in some studies (Currie et al. 2013; Villanueva et al. 2005; Yang et al. 2002). Results indicated that contamination in water consumed by mothers, such as lead and chlorination disinfection by-products and chlorinated solvents, might increase the LBW risk in offspring (Bove et al. 1995; Bove, Shim, and Zeitz 2002; Cleveland et al. 2008). A couple of studies have found that maternal exposure to less surrounding green space was also associated with decreases in infants' birth weight (Dadvand et al.

2012; Laurent, Wu, Li, and Milesi 2013). There was also evidence of higher LBW risk for mothers residing in the vicinity of industrial installations, such as pharmaceutical, mining, biocides, and animal waste management plants (Castello et al. 2013). Desert dust was suspected to be a risk factor for LBW as well, but no statistically significant associations have been found (Dadvand et al. 2011). There has been no clear evidence of association between potential maternal exposure to ionizing radiation in the vicinity of nuclear facilities and LBW in offspring, but many residents were still concerned that living near a nuclear facility may affect the health and safety of their families (Akhir and Alamgir 2012). Consequently, additional studies are necessary to examine if living near nuclear facilities is an environmental risk factor for LBW in offspring.

This research will focus on two categories of environmental factors, namely (1) ambient air pollution (AAP), and (2) ionizing radiation near nuclear facilities (Figure 1.2).

1.2. Problem Statement

There are some limitations in the literature on environmental risk factors for LBW. Specifically, past studies examining associations between ambient air pollution exposure/radiation exposure near nuclear facilities and LBW have several limitations. First, six criteria air pollutants (CAPs), including particulate matter (PM2.5, PM10), ozone (O3), nitrogen dioxide (NO2), sulfur dioxide (SO2), carbon monoxide (CO), and lead (Pb) (U.S. EPA 2011), have been found to be associated with LBW in numerous studies (Bell, Ebisu, and Belanger 2007; Darrow, Klein, Sarnat, et al. 2011; Ebisu and Bell 2012; Geer, Weedon, and Bell 2012; Maisonet et al. 2001; Parker et al. 2005; Wang et al. 1997). However, few studies have investigated the association between other air

pollutants and LBW. Second, the various exposure windows of air pollution used in previous studies made it difficult to reach a univocal conclusion on air pollution-LBW association. “Critical exposure windows” are limited temporal intervals during which maternal exposure to air pollutants may have the greatest potential to affect the birth weight in offspring. However, most of the published studies used predefined exposure windows (e.g. entire pregnancy, trimesters, months), which restricted the discovery of more critical exposure windows that might have different starting times and time durations. Third, few studies considered exposure windows covering a time period before conception. Fourth, there has been little research about the influence of potential maternal exposure to ionizing radiation near nuclear facilities on LBW in offspring.

1.3. Objectives and Research Questions

The purpose of this dissertation is to contribute to the theoretical literature on human environmental science and spatial epidemiology by examining the environmental risk factors associated with LBW using massive georeferenced data in Texas. More specifically, this study will utilize geographic information systems (GISs) and spatio-temporal analysis methods to investigate the associations between maternal exposure to ambient air pollution/maternal residential proximity to nuclear facilities and LBW in offspring in Texas.

The research aims to address the following questions:

(1) Is there any association between maternal exposure to some chemicals released into the air from Toxic Release Inventory facilities (TRI chemicals) and LBW in offspring based on the analysis of massive georeferenced data?

(2) Is there any association between maternal exposure to some chemicals monitored by the Texas Commission on Environmental Quality air quality monitors (TCEQ chemicals) and LBW in offspring based on the analysis of massive georeferenced data? If any TCEQ Chemicals-LBW associations exist, do these associations vary spatially and/or temporally? What are the most critical exposure window(s) for each TCEQ chemical?

(3) Is maternal residential proximity to nuclear facilities associated with LBW in offspring? If the association exists, does it vary with different distance thresholds?

The research proposes three hypotheses to answer the research questions defined above:

Hypothesis 1: There is no association between maternal exposure to any TRI chemicals and LBW in offspring.

Hypothesis 2: There is no association between maternal exposure to any TCEQ chemicals and LBW in offspring. There is no spatial and temporal variation in all the TCEQ Chemicals-LBW associations.

Hypothesis 3: There is no association between maternal residential proximity to the nuclear facilities and LBW in offspring.

1.4. Environmental Risk Factors for LBW Research and Geography

One important theme in geographic research is about society, environment, and the relationships between the two. Based on the history of geography, one can discover that geographic research has gone through different stages, including cosmology, region differentiation, environmental determinism, cultural determinism, and landscape study. With an extensive investigation on these different stages of geography, one can note that the themes of geography include space, place, person, and relationships among them. Pattison (1964) categorized geographic research into four traditions. These four traditions are spatial tradition, area study tradition, man-land tradition, and earth science tradition. This section will use the four-tradition structure to discuss how this dissertation research fits within the broader geography literature.

The spatial tradition focused on discovering the pattern and distribution of spatial entities through analyzing their geometry and movement. In this tradition, the space is considered as a pure container. The spatial entities (physical objects or human) inside are simplified to geometrical objects in the container. This tradition is improved a lot with the emerging of quantitative geography and Geographic Information Science (GIScience). The area study tradition considers area differentiation as the research topic. With comprehensive understanding of an area, researchers can discover the social-cultural causes of certain phenomenon. Additionally, through comparison of different areas, researchers can understand the different underlying mechanisms. The man-land tradition is also known as human-environmental tradition. This tradition concentrates on the mutual relationships between humans and the environment. The earth science

tradition studies the earth, air, and water on the planet. This tradition is closely related to physical geography research.

This dissertation research covered three traditions of geographic research. First, this research modeled the maternal residential exposure to ambient air pollution/ionizing radiation and analyzed the spatial pattern of the exposure and LBW cases/controls. Study area (Texas) was considered as a container; the air pollution emission source, air quality monitoring sites, nuclear facilities, newborns, and their mothers were conceptualized as points for analysis. These simplifications follow the spatial tradition accurately. Second, while performing statistical analysis to discover association between environmental risk factors and LBW, this research adjusted for all the social-cultural factors. Understanding these comprehensive factors in the research area consisted an important part of the area study tradition. Third, the research topic about the environmental risk factors for LBW was itself a man-land tradition topic. Humans ignored the environment by building toxic release facilities and nuclear facilities. These facilities caused air pollution and ionizing radiation in the environment. Consequently, the air pollutants and ionizing radiation reached the population and caused adverse health outcomes. Therefore, the investigation of the mutual influences in this research accurately followed the man-land tradition.

More specifically, this dissertation was also a study in health geography. In traditional health geography, GIS was used for mapping disease information, analyzing spatial pattern of diseases, identifying risk factors related to certain spatial patterns, analyzing health care access, and locating health care services. The present study also used GIS to perform some of these analyses. In this dissertation, the temporal aspects were taken into account in exposure assessment involving different time windows, and

geocomputational methods were used for parameter calibration in the model for air pollution exposure assessment.

2. LITERATURE REVIEW

2.1. Birth Weight Research

This research conducted a literature search in the database of Web of Science (WoS) of the Institute of Scientific Information (ISI). In epidemiological analysis, birth weight can either be measured as a continuous variable or dichotomized into low birth weight and normal birth weight using 2,500 grams (or 5.5 pounds) as a threshold. Considering different measurements used, the key words for literature searching were not restricted to low birth weight (LBW). The key words used in this research included "birth weight," "low weight * birth," "birthweight," and "low-birth-weight." A total of 75,833 publications about birth weight research were returned.

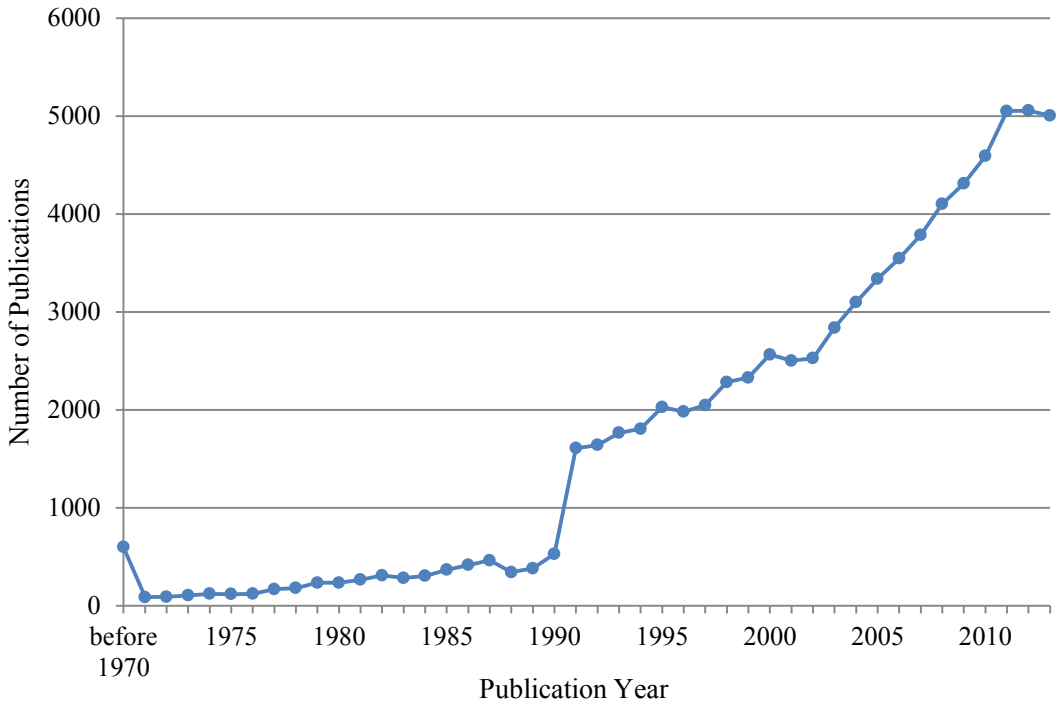

Figure 2.1 Number of publications on birth weight research (Web of Science database, February 17, 2014)

The publications on birth weight research dated back to 1904. Figure 2.1 illustrates the growing trend of the related literature. Before 1990, the amount of studies per year was comparatively stable, which showed a slightly increasing trend. In 1991, the number of birth weight publications jumped from 500 to around 1,500 per year. The sudden increase in publications indicated that the topic started to become popular. After 1991, more and more people as well as institutes were involved in birth weight research. The publication quantities kept increasing steadily until 2010. In recent years (2011-2014), the number stayed around 5,000. Based on this trend, "birth weight" is still a very hot topic, which deserves research nowadays.

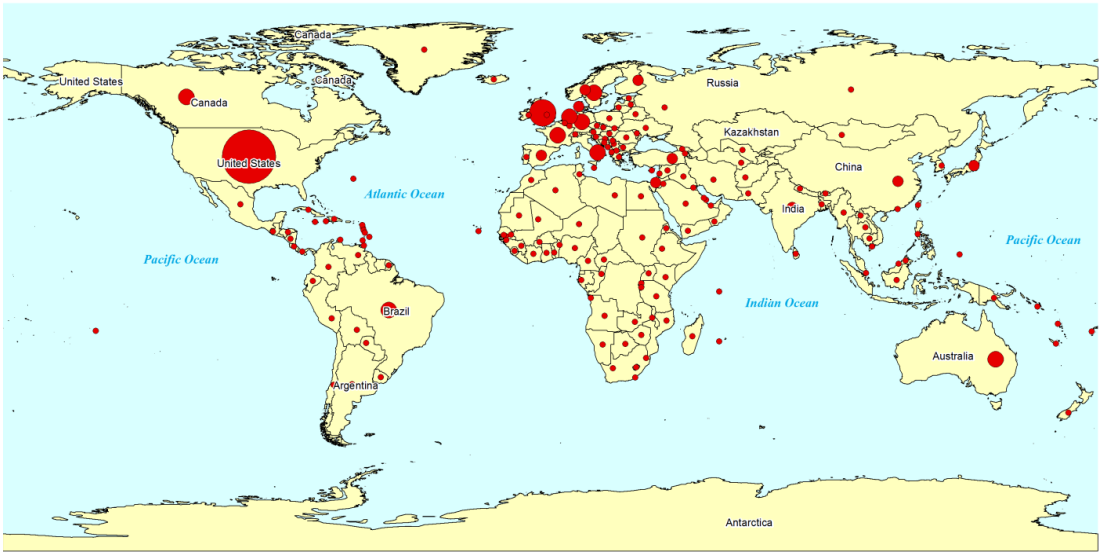

Figure 2.2 Geographic distribution of publications about birth weight (Web of Science database, February 17, 2014).
(Sizes of points are proportionate to the number of publications in countries/regions/former countries)

The topic, birth weight, has attracted global research interest. In total, 177 countries/regions/former countries have published research on birth weight (Figure 2.2). However, the publications were not evenly distributed across continents. Most publications were from North America and Europe. Studies from the United States

consist of 37.25% of the total literature (Table 2.1). The top 20 countries/regions/former countries in publication quantities accounted for 96.8% of the total literature (Table 2.1). Therefore, centers of birth weight research were located in these areas. Possible reasons for this clustered geographic distribution included the data availability and completeness, the number of research facilities, people's awareness in different countries/regions/former countries, etc.

Table 2.1 Publication distribution of birth weight research

Countries/Regions	Records	Percentage	Countries/Regions	Records	Percentage
United States	28,246	37.25	Japan	1,993	2.63
United Kingdom	9,798	10.52	Denmark	1,638	2.16
Canada	4,269	5.63	Spain	1,548	2.04
Australia	3,943	5.20	India	1,443	1.90
Germany	3,529	4.46	Finland	1,317	1.74
Netherlands	2,801	3.69	Israel	1,280	1.69
France	2,696	3.56	China	1,232	1.62
Italy	2,547	3.36	Norway	1,206	1.59
Sweden	2,430	3.20	Turkey	1,163	1.53
Brazil	2,296	3.03	New Zealand	967	1.28

2.2. Environmental Risk Factors for LBW: Ambient Air Pollution

2.2.1. Ambient Air Pollution and LBW

The ambient air pollution (AAP), also known as outdoor air pollution, is present in all places at all times (Polichetti et al. 2013). It has been becoming a global public health problem (Romao et al. 2013; Shannon et al. 2004). Many studies have found exposure to AAP was associated with different health outcomes, such as respiratory and cardiovascular diseases, and even mortality (Bobak and Leon 1999; Polichetti et al. 2013; Romao et al. 2013).

In common sense, babies were considered more vulnerable than children and adults, so it have raised questions as to whether AAP exposure during pregnancy could also affect birth outcomes (Bobak and Leon 1999). Since the mid-1990s, many studies have investigated the possible adverse influence of AAP on birth outcomes, including low birth weight, small for gestational age, preterm birth, and birth defects (Ritz and Wilhelm 2008; Srám et al. 2005). According to these studies, an emerging body of evidences suggested that the maternal exposure to AAP during pregnancy was associated with birth outcomes (Darrow, Klein, Strickland, et al. 2011; Hansen et al. 2007; Ling and Yun-hui 2007; Sharkhuu et al. 2010; Veras et al. 2010).

As one of the adverse birth outcomes, LBW has also gained attentions in the scientific community. Studies from different places around the world have shown evidences that AAP exposure might interfere with weight gain in the fetus (Ebisu, Belanger, and Bell 2008; Madsen et al. 2010; Mannes et al. 2005; Medeiros and Gouveia 2005; Parker and Woodruff 2008; Stankovic, Mitrovic, and Zivadinovic 2011; Yorifuji et al. 2013). However, the results were not consistent across studies. The inconsistency might arise from different aspects, including the type of ambient air pollutants in research, the choice of exposure assessment methods, and the selection of exposure windows. In the following sections, this research reviewed these three aspects separately.

2.2.2. Ambient Air Pollutants in the Literature

Refining the birth weight related literature with a key word “air,” about 1,299 publications were returned from the database of Web of Science (WoS). Through manually checking, 230 publications that were relevant to the research questions were

Table 2.2 Ambient air pollutants in birth weight literature

Criteria air pollutants (CAPs) and related air pollutants (parameters)			Other air pollutants (parameters)		
Pollutant (parameter)	No. Of publications	Examples	Pollutant (parameter)	No. Of publications	Examples
PM_{10}	50	(Kim et al. 2007; Maisonet et al. 2001; Salam, Millstein, and Li 2005)	Benzene, Toluene, Ethyl benzene, and Xylene (BTEX)	9	(Aguilera et al. 2009; Estarlich et al. 2011; Zahran et al. 2012)
$PM_{2.5}$	48	(Ebisu and Bell 2012; Hyder et al. 2014; Parker et al. 2005)	Polycyclic aromatic hydrocarbons (PAHs)	9	(Perera et al. 2003; Sanyal et al. 2007; Wilhelm et al. 2012)
NO_2	46	(Darrow, Klein, Strickland, et al. 2011; Estarlich et al. 2011; Lee et al. 2003)	Benzo[a]pyrene (B[a]P)	3	(Al-Saleh et al. 2013; Gladen et al. 2000; Perera et al. 2004)
CO	38	(Bell, Ebisu, and Belanger 2007; Morello-Frosch et al. 2010; Ritz and Yu 1999)	Polycyclic organic matter (POM)	2	(Vassilev, Robson, and Klotz 2001a, 2001b)
SO_2	36	(Cho, Lee, and Kim 2013; Wang et al. 1997; Williams et al. 2007)	Air pollution index based on coal consumption	1	(Bobak, Richards, and Wadsworth 2001)
O_3	29	(Chen et al. 2002; Geer, Weedon, and Bell 2012; Laurent, Wu, Li, Chung, et al. 2013)	Cadmium	1	(Currie and Schmieder 2009)
Total suspended particulate (TSP)	8	(Bobak 2000; Lee et al. 2002; Wang et al. 1997)	Chlorine	1	(Dimitriev, Dimitriev, and Konstantinova 2006)
Nitric oxide (no)	6	(Brauer and Lencar 2008; Wilhelm et al. 2012; Ghosh et al. 2012)	Epichlorohydrin	1	(Currie and Schmieder 2009)
Nitrogen oxides (no_x) [a]	6	(Bobak 2000; Bobak and Leon 1999; Wilhelm et al. 2012)	Ammonia (NH_3)	1	(Dimitriev, Dimitriev, and Konstantinova 2006)
Lead	4	(Berkowitz et al. 2006; Williams et al. 2007)	Phenol	1	(Dimitriev, Dimitriev, and Konstantinova 2006)
PM	5	(Kannan et al. 2006; Siddiqui et al. 2008)	Polychlorinated biphenyls (PCB)	1	(Nieuwenhuijsen et al. 2013)
Black carbon[b]	3	(Brauer and Lencar 2008; Paciorek 2010)	Soot	1	(Gehring, Wijga, and Fischer 2011)
Black smoke[c]	2	(Pearce et al. 2012; Stankovic, Mitrovic, and Zivadinovic 2011)	Welding fumes (WF) and Metal dusts or fumes (MD/F)	1	(Quansah and Jaakkola 2009)
Pollutant Standard Index (PSI) [d]	1	(Janghorbani and Piraei 2013)			
Total	282		Total	32	

[a] NO_x is a generic term for mono-nitrogen oxides NO and NO_2;
[b] A component of fine particulate matter (http://www.epa.gov/blackcarbon/basic.html);
[c] A historic measure of airborne particulate matter;
[d] PSI for five major pollutants (CO, O_3, NO_2, SO_2, PM_{10}). PSI converts air pollution concentrations to a simple number between zero and 500 and assigns descriptive terms such as "good" or "moderate" to that value.

retained. In these studies, various ambient air pollutants were examined as potential environmental risk factors for LBW (Table 2.2).

The ambient air pollutants (parameters) can be divided into two categories: (1) criteria air pollutants (CAPs) and related air pollutants (parameters) and (2) other air pollutants (parameters). A large number of studies (282) have linked CAPs and related pollutants (parameters) with LBW, but much less studies (32) have focused on the importance of other air pollutants (parameters) (Wilhelm et al. 2012).

In many studies, the CAPs, including $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, CO, and Pb, were considered as risk factors for LBW. For example, Salam, Millstein, and Li (2005) found that PM_{10} exposure was associated with increased LBW levels; Bell, Ebisu, and Belanger (2007) discovered that even low level exposure to CO during the first and third trimesters might increase the risk of LBW. Estarlich et al. (2011) proved that maternal exposure to NO_2 was related to decreases in birth weight. Besides the CAPs, some related air pollutants were also in the first category, including black carbon (Brauer and Lencar 2008; Paciorek 2010), black smoke (Pearce et al. 2012; Stankovic, Mitrovic, and Zivadinovic 2011), total suspended particle (TSP) (Bobak 2000; Lee et al. 2002; Wang et al. 1997), etc. These air pollutants were either components or combination of the CAPs.

The second category of ambient air pollutants (parameters) has been less frequently investigated. Most pollutants were mentioned in no more than three studies, except for BTEX (Benzene, Toluene, Ethyl benzene, and Xylene) and PAHs (Polycyclic Aromatic Hydrocarbons). The BTEX and PAHs exposure were considered as potential risk factors for less than ten times in the literature. For example, Slama et al. (2009)

found that maternal exposure to airborne benzene was associated with decreases in birth weight. Aguilera et al. (2009) linked the exposure of BTEX with the reduced birth weight. Gladen et al. (2000) concluded that there was not enough evidence supporting the PAH exposure-LBW association.

There was a large gap between the LBW-related publication quantities of the two categories. One reason was that the CAPs have demonstrated health impacts for numerous health outcomes other than the LBW, including respiratory symptoms, hospitalization for heart or lung diseases and even premature death (U.S. EPA 2015b). This situation inspired many researchers to explore the impact of CAPs for LBW. The other reason for the quantity difference was the data availability. The monitoring networks of CAPs had larger spatial coverage and finer spatial-temporal resolution. Therefore, the exposure to these ambient air pollutants were easier to be estimated from the monitoring data (further discussion in 2.2.3), which also created convenience for further epidemiological analysis. As a result, researchers tended to focus on the CAPs and related pollutants in air pollution-LBW studies.

Although around fifteen pollutants (parameters) other than the CAPs were listed in the second category, these pollutants only covered a small part of all pollutants in the air. In the Toxic Release Inventory (TRI) program, releases of over 650 chemicals into the air have been reported (U.S. EPA 2013a). The Texas Air Monitoring Information System (TAMIS) of Texas Commission on Environmental Quality (TCEQ) also included 393 parameters (367 of which were ambient concentrations of chemicals in the air) for each TCEQ air quality monitoring site (TCEQ 2015). All these TRI chemicals and TCEQ chemicals could possibly have adverse effects on pregnancy outcomes. Therefore, this

research will investigate the association between maternal exposure to these chemicals and LBW in offspring.

2.2.3. Air Pollution Exposure Assessment Methods

Exposure assessment is one of the major challenges when investigating the association between exposure to ambient air pollution and LBW in offspring (AAP-LBW association) (Ribeiro et al. 2010). A comparison of commonly used air pollution exposure assessment methods is shown in Table 2.3. According to Nieuwenhuijsen et al. (2006), methods for air pollution exposure assessment could be categorized into two major categories: direct methods and indirect methods.

Direct methods measure air pollution exposure by individual monitoring. Techniques such as biomarker testing and portable monitoring equipment are used in this method. Direct methods are considered the most accurate way in air pollution exposure assessment. However, the methods are vulnerable to sample selection bias (Duan and Mage 1997). More importantly, these methods are expensive, labor-intensive and time-consuming in almost all cases (Forastiere and Galassi 2005; Gray, Edwards, and Miranda 2010). These characteristics restrict the usage of direct methods in large population-based study and long-term monitoring. Nevertheless, the individual monitoring data are still very useful as a benchmark for validating other exposure assessment models.

Indirect methods, also known as exposure modeling, are "logical or empirical construct which allow estimation of individual or population exposure parameters from available input data" (WHO 2000). According to the different sources of input data,

Table 2.3 Comparison of air pollution exposure assessment methods

Categories	Methods		Examples	Key advantages	Key disadvantages
Direct methods	Individual monitoring		• Biological monitoring • Portable equipment measuring	• Most accurate estimation, "gold standard" • Useful as benchmark	• Expensive • Time consuming • Labor-intensive • Sample selection bias
Indirect methods	Ambient monitor-based methods	Direct surrogate model	• Data from closest monitors as a surrogate for exposure	• Simple • Directly use the monitoring data	• Rely on the availability of monitoring data • Require proper radius of area surrounding monitors
		Interpolation model	• IDW • Spline • Kriging	• Generate continuous surface which can simulate sources and sinks of air pollution concentration	• Rely on the availability of monitoring data
	Pollution source-based methods	Air dispersion model (Self-prepared)	• Human Exposure Model-3 (HEM-3) • Assessment System for Population Exposure Nationwide (ASPEN) • CALPUFF	• Consider various factors and different types of pollution sources • More extensive spatial coverages than ambient monitor-based methods	• Extensive data requirement • Time consuming • Hard to implement in large areas over multiple years • Estimates bring uncertainty. • Estimating some pollutants better than others.
		Air dispersion model (Public dataset)	• National-scale Air Toxics Assessment (NATA)	• Consider various factors and different types of pollution sources • Ready for further analysis, easy to acquire, avoid long computing time	• Limited temporal coverage • Restricted spatial resolution
		Proximity model	• Emission Weighted Proximity Model (EWPM)	• Simple to implement • Low data requirement • Appropriate for exploratory analysis prior to more sophisticated investigations	• Exposure misclassification

indirect methods can be divided into two groups: ambient monitor-based methods and pollution source-based methods.

The ambient monitor-based methods estimate human exposure using data collected from ambient air monitors. The methods can be further divided into two subgroups: direct surrogate model and interpolation model. The direct surrogate model uses data from ambient monitors as a surrogate for individual or community-level exposure to air pollutants (Bell 2006). In this model, concentrations of a given air pollutants are assumed to be spatially homogeneous in the areas surrounding the monitors (Gray, Gelfand, and Miranda 2011). Therefore, it is very important to define a proper radius of the surrounding area in this model. If the radius were too large, the homogeneity assumption would be violated, and measurement errors would be introduced into the results. If the radius were too small, study population would be restricted to people living very close to the monitors, which would cause selection bias. Moreover, the reduced sample size in the small areas surrounding limited monitors might reduce the study power of further statistical analysis (Kloog et al. 2012). Most large-scale studies of the relation between air pollution exposure and health effect utilized this model, because this model can conveniently use the monitoring data without further processing. The interpolation model can generate a continuous surface of air pollution concentration based on monitor measurements using techniques such as IDW (Brauer and Lencar 2008), spline (Wilson and Zawar-Reza 2006), and Kriging (Briggs et al. 1997). The continuous surface can simulate the sources and sinks of air pollution concentrations. However, as ambient monitor-based methods, both direct surrogate model and interpolation model rely on the availability of relatively dense monitoring networks. If study areas had inadequate spatial

or temporal coverage of monitors (e.g. rural area), exposure would be difficult to be estimated and would be less accurate (Bell 2006).

The pollution source-based methods model the human exposure based on emission data from air pollution sources. Generally, two types of models, air dispersion model and proximity model, are included.

Air dispersion models generally use air emission data and meteorological data as input data, and estimate the concentrations of air pollutants over space and time through numerical processing (Zou et al. 2009a). Examples of these models include Human Exposure Model-3 (HEM-3) (U.S. EPA 2013b), Assessment System for Population Exposure Nationwide (ASPEN) (U.S. EPA 2010), and CALPUFF (Levy et al. 2002). Air dispersion models have been used as a primary method for assessing human exposure intensities in urban areas (Kousa et al. 2002). In areas with sparse monitoring network, air dispersion models can also provide more complete pollutant concentration profiles than ambient monitor-based methods (Clench-Aas et al. 1999). However, because air dispersion models only simulate the dispersion process with mathematical models, the estimated concentrations also include some uncertainties. Another advantage of air dispersion models is that various factors (e.g. meteorological factors, air temperature, topography, and road type) and different types of pollution sources (point, line, and area sources) can be taken into account in the modeling process (Zou et al. 2009a). However, in practice, it is often difficult to satisfy the extensive data requirements of air dispersion models for studies that require environmental data covering large geographic areas over multiple years. Therefore, the air dispersion models are better at estimating some air

pollutants than others, which depends on the availability of model input data and the ability of models to simulate the dispersion and atmospheric chemistry.

For some air pollutants, there are exposure intensity estimates covering large geographic areas. One source is the National-Scale Air Toxics Assessment (NATA) datasets. These datasets are available to the public and can be easily acquired. Another benefit of the NATA data is that it retains the advantages of air dispersion models. However, the estimated air pollution exposure intensities form NATA only have limited temporal coverage and restricted spatial resolution. For instance, the NATA datasets only cover four non-consecutive years 1996, 1999, 2002, and 2005 as of this writing. The finest spatial resolution of the NATA dataset is at the census tract level.

Proximity models are the most straightforward approach to estimate air pollution exposure intensities around a given pollution source. The models use proximity as a proxy for exposure intensity estimation, assuming that the exposure intensities decline with increasing distances from a pollution source. Proximity models are simple to implement and require less data than other pollution source-based methods. These characteristics make proximity models very suitable for estimating exposure intensities in large geographic areas over multiple years. Moreover, when the relation between air pollutants and human health effects is not clear, proximity models are appropriate for exploratory analysis prior to more sophisticated investigations (Zou et al. 2009a). Traditional proximity models (TPMs) may suffer from exposure misclassification in the modeling results when distance to the nearest pollution source is used as a proxy in the model. Zou et al. (2009b) proposed an Emission Weighted Proximity Model (EWPM), which can mitigate this key weakness of the TPM. Unlike the TPMs which only consider

distance of a receptor to the closest emission source, the EWPM additionally took into account emission rate and emission time of all known sources potentially affecting a receptor at a specific location. Based on the results of an evaluation using data in two Texas counties over a one-year period, Zou et al. (2009b) suggested that the EWPM produces more accurate estimates than TPMs in estimating exposure intensities of individuals.

In summary, each exposure assessment method has its advantages and disadvantages. Some methods work better for some air pollutants than others, which depends on the availability of monitoring data for ambient monitor-based methods, the availability of air emission data for pollution source-based methods, the spatial heterogeneity of pollutant concentrations for direct surrogate model, or the simulation ability of dispersion and atmospheric chemistry for air dispersion model. There is not a universal criterion for selecting the best model for air pollution exposure assessment.

2.2.4. Exposure Windows

Around twenty different exposure windows were covered in the previous research (Table 2.4). When different exposure windows were considered, many studies reported totally different AAP-LBW association (Geer, Weedon, and Bell 2012; Morello-Frosch et al. 2010; Pearce et al. 2012). As a result, it would be difficult to reach a consistent conclusion. In order to integrate all these results and find the critical exposure window during which the AAP-LBW association were the strongest, a standardized protocol for critical exposure window exploration is required in this study.

Table 2.4 Air pollution exposure windows investigated in birth weight research

Exposure windows	Number of publications	Examples
Whole year	1	(Parker and Woodruff 2008)
9-months	1	(Parker and Woodruff 2008)
Whole pregnancy	94	(Bell, Ebisu, and Belanger 2007)
Each trimester	54	(Ebisu and Bell 2012)
The first trimester	3	(Ha et al. 2001)
The second trimester	1	(Gehring, Wijga, and Fischer 2011)
The third trimester	6	(Darrow, Klein, Strickland, et al. 2011)
Each month	7	(Hansen et al. 2007)
The first 3 months	1	(Brauer, Lencar, and Tamburic 2006)
The last 3 months	2	(Brauer and Lencar 2008)
The first month	3	(Le, Batterman, and Wirth 2012)
The last month	7	(Ghosh et al. 2012)
During birth month	1	(Trasande et al. 2013)
The first 30 days	1	(Berrocal, Gelfand, and Holland 2011)
The first 60 days	1	(Berrocal, Gelfand, and Holland 2011)
The last 30 days	2	(Berrocal, Gelfand, and Holland 2011; Janghorbani and Piraei 2013)
The last 60 days	1	(Berrocal, Gelfand, and Holland 2011)
3 months before pregnancy	1	(Quansah and Jaakkola 2009)
Prior to conception (animal test)	1	(Veras 2009)

Though the quantities were large, the time durations and starting times of the exposure windows in the literature were limited (Figure 2.3). Most studies (94 publications) used the whole pregnancy as the exposure window for analysis, while many other studies (54 publications) considered the difference of associations across trimesters. Other exposure windows were considered in only a small portion of the publications. Therefore, the time durations of exposure window were usually limited to 30 days, 60 days, a trimester, or whole pregnancy. Furthermore, except for a few studies, the exposure windows usually started from limited time-spots, e.g. the beginning of a month, the beginning of a trimester, the beginning of a pregnancy. The limited choices of exposure windows might restrict the exploration of more critical exposure windows with

more flexible time durations and starting times. For each study, the exposure windows were usually defined before the analysis, so the time durations and starting times would not change during the whole study. However, if without any prior knowledge about starting times and time durations of critical exposure windows, it would be difficult to accurately include the critical exposure windows in the predefinition. As a result, flexible exposure windows that vary continuously across time are required in this research. Warren et al. (2012) has used this kind of exposure window to explore the association between air pollution exposure and preterm birth, but no existing research has done similar analysis on low birth weight.

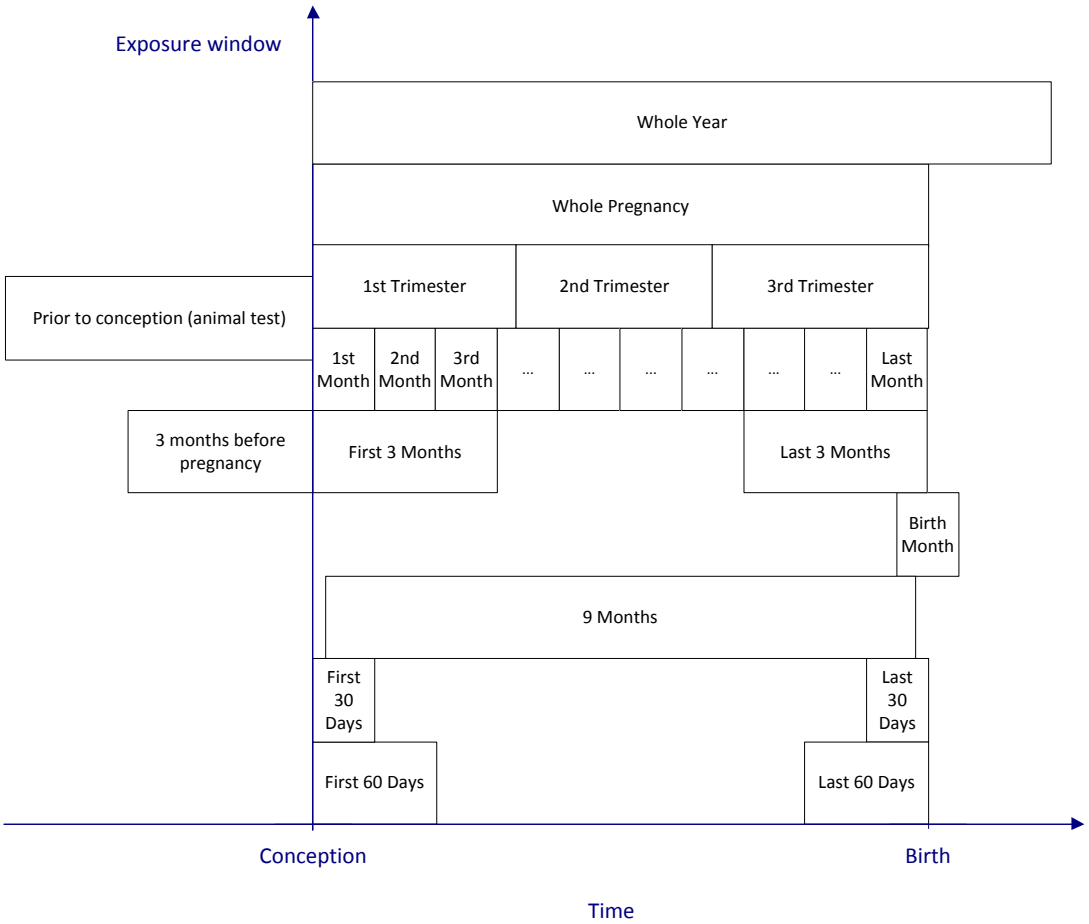

Figure 2.3 Exposure windows of air pollution investigated in birth weight research

According to Figure 2.3, most studies only considered the maternal exposure after conception, except for two studies (Quansah and Jaakkola 2009; Veras 2009). Quansah and Jaakkola (2009) concluded that the exposure to combination of welding fumes (WF) and metal dusts or fumes (MD/F) during the three month before pregnancy were related to higher LBW risk. The animal experiment results of Veras (2009) reinforced the idea that maternal exposure to air pollution was linked to negative pregnancy outcomes, even if the exposure occurred only before conception. Therefore, the exposure windows before conception should also be included in the analysis of AAP-LBW association.

2.3. Environmental Risk Factors for LBW: Nuclear Facilities

More and more nuclear facilities have been built to meet the increase of demand on electricity. A total of 100 commercial nuclear power reactors were in operation in the United States in 2015 (U.S. NRC 2015a). The repeated occurrences of serious nuclear power plant accidents, including Three Mile Island (1979), Chernobyl (1986), and Fukushima Daiichi (2011), etc., have raised the public concerns (Huang et al. 2013). People worry not only about the environmental impact of the nuclear facilities, but also about the facilities' influence on human health and safety. Many studies have investigated the different health outcomes of close residential proximity to nuclear facilities using statistical analysis. As a result, this research will review the literature from the following three aspects: environmental impact, health outcomes, and analysis methods.

2.3.1. Nuclear Facilities and Environmental Impact

Nuclear facilities are suspected to have adverse impact on surrounding environment, such as the forest ecosystem, water, and air.

The influence of nuclear facilities on the forest ecosystem have been examined through the distribution of radionuclides (Carbon-14, Caesium-137, Cobalt-60, etc.) activity concentrations in the top soil, plant species, and tree rings samples in the vicinity of nuclear facilities. Some studies have discovered negative influences of nuclear facilities on the forest ecosystem. Magnusson et al. (2004) found that Carbon-14 level in the surroundings of nuclear power plants were higher than the reference area. This kind of excess value was associated with the Carbon-14 discharge from nuclear power plants (Wang, Xiang, and Guo 2012a). Moreover, moss and vegetation samples also showed that Carbon-14 activity values decreased with increasing distance from nuclear facilities (Dias et al. 2008; Wang, Xiang, and Guo 2012b). In addition, some studies found that the nuclear facilities had little influence on the forest system. The Carbon-14, Caesium-137, and Cobalt-60 activity values showed no accumulation in the soil surface near nuclear facilities (Dias, Stenstrom, et al. 2009; Luksiene et al. 2012; Roussel-Debet et al. 2006). In annual tree rings samples, Janovics et al.(2013) only discovered slight increase in Carbon-14 level which was not statistically significant. As a result, it is inconclusive whether nuclear facilities have negative or neutral influence on the surrounding forest ecosystem.

Findings of nuclear facilities' influences on surrounding water were also inconsistent. Ilyinskikh et al. (2000) concluded that radiochemical production wastes released into the water had caused extensive contamination. However, Sladekova,

Proksova, and Toth (2000) found that the wastewater from nuclear facilities did not affect waters of Vah and Hron rivers negatively.

Several studies have discovered that air around nuclear facilities was also influenced. For example, nuclear facilities have been continuously releasing Carbon-14 in different chemical forms (CO2, CO and hydrocarbons) (Dias, Telles, et al. 2009). These airborne effluents of radionuclide have caused the excess values measured in the nearby air samples (Stenström, Skog, and Thornberg 1998). However, Dias et al. (2009) concluded that the excess values were not related to the emission from the vent stacks of nuclear facilities.

2.3.2. Nuclear Facilities and Health Outcomes

Because of the environmental impact near the nuclear facilities, general public were concerned that the ionizing radiation and radioactive waste from the nuclear facilities might also affect human health (Akhir and Alamgir 2012). This growing risk perception had encouraged research on the relation between some health outcomes and close residential proximity to nuclear facilities. Table 2.5 shows the study designs and conclusions of selected publications on residential proximity to nuclear facilities and health outcomes.

Many health outcomes near nuclear facilities have been investigated in the literature (Table 2.5). Most studies focused on childhood cancer, especially leukemia (a type of cancer of the blood or bone marrow). A famous example was the Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK) case-control study in Germany, which indicated that children in the areas around nuclear power plants had a statistically

Table 2.5 Selected publications on residential proximity to nuclear facilities and health outcomes

Studies	Distance thresholds of residential proximity to nuclear power plant (NPP) or Nuclear facility (NF)	Health outcomes	Regions	Conclusions
(Mangones, Visintainer, and Brumberg 2013)	5 miles, 10 miles, 15 miles, 20 miles	Low birth weight, congenital anomalies , and prematurity	USA	The prevalence of defects, low birth weight, and prematurity were not related to proximity to the nuclear power plant.
(Wang et al. 2010)	"Plant-vicinity" and "Non plant-vicinity" group (counties), around 20 km	Stillbirth, premature birth, low birth weight, congenital deficiencies	Taiwan	Residence in the vicinity of a nuclear power plant is not a significant factor which will cause abnormal health situations during pregnancy.
(Slama et al. 2008)	The "canton" (electoral ward) of Beaumont-Hague, France	Monthly probability of pregnancy, occurrence of involuntary infertility, miscarriage, birth weight	France	No increased risk of adverse reproductive life events compared with the reference area.
(Bithell and Murphy 2013)	5 km	Childhood Leukemia and non-Hodgkin Lymphoma (LNHL)	Great Britain	Little evidence of an increase in risk of Childhood LNHL in the vicinity of a NPP
(Spycher et al. 2011)	5 km, 10 km , 15 km	Childhood cancer	Switzerland	Little evidence of an association between residence near NPPs and the risk of leukemia or any childhood cancer
(Scherb and Voigt 2011)	35 km	Sex odds	Germany, Switzerland	The sex odds increase significantly in the range of 0.30% to 0.40% during NF operating time.
(Queisser-Luft et al. 2011)	10 km	Birth defects	Germany	The prevalence of birth defects in the regions surrounding NPPs: (1) was not increased compared to those of the comparison region, within the study region, (2) showed no upward trend with decreasing distance.
(Levin 2008)	5 mile	Thyroid Cancer	USA	No causal link of thyroid cancer to the Three Mile Island accident.

Table 2.5-Continued

Studies	Distance thresholds of residential proximity to nuclear power plant (NPP) or Nuclear facility (NF)	Health outcomes	Regions	Conclusions
(McLaughlin and Clarke 1993)	25 km	Childhood leukemia	Canada	The observed number of leukemia deaths was slightly greater (not statistically significant) than expected during the period when the facilities operated.
(Sermage-Faure et al. 2012)	5 km, 20 km	Childhood acute leukemia (AL)	French	A possible excess risk of AL in the close vicinity of French NPPs in 2002-2007, which cannot be explained by NPP gaseous discharges.
(Mataloni et al. 2012)	7 km	Cancer incidence and mortality	Italy	Living close to the NPP was not associated with mortality for causes related to radiation exposure.
(Ahn, Li, and Grp 2012)	5 km, 30 km	Cancer risk	Korea	No evidence for increased risk of cancer due to radiation from NPPs.
(Kaatsch and Spix 2008)	5 km	Childhood leukemia	Germany	A statistically significant odds ratio of 2.19 (lower 95% confidence limit : 1.51) for residential proximity within 5 km compared to residence outside this area.
(Spix et al. 2008)	5 km	Childhood cancer	Germany	The inner 5- km zone shows an increased risk (odds ratio 1.47; lower one-sided 95% confidence limit 1.16). The effect was largely restricted to leukemia.
(Hoffmann 2007)	5 km	Childhood leukemia	Germany	The incidence in this region is significantly higher than the childhood leukemia incidence for Germany as a whole.
(Mangano et al. 2003)	30 miles (48 km)	Childhood cancer mortality, leukemia incidence	USA	Incidence is particularly elevated for leukemia. Childhood cancer mortality exceeds the national average in 7 of the 14 study areas.

Table 2.5-Continued

Studies	Distance thresholds of residential proximity to nuclear power plant (NPP) or Nuclear facility (NF)	Health outcomes	Regions	Conclusions
(Silva-Mato et al. 2003)	10 km , 20 km, 30 km	Cancer risk	Spain	There is an association between proximity of residence to Trillo (NPP) and cancer risk.
(Lopez-Abente et al. 1999)	30 km, 50 km	Leukemia, lymphomas, and myeloma mortality	Spain	None of the nuclear power plants registered an excess risk of leukemia-induced mortality in any of the surrounding areas.
(Sharp et al. 1996)	25 km	Childhood leukemia and non-Hodgkin's lymphoma	Scotland	(1) No increased risk of childhood leukemia and non-Hodgkin's lymphoma around nuclear sites in Scotland. (2) No trend of decreasing risk with distance from NFs.
(Morris and Knorr 1996)	4 mile (6.4 km)	Adult leukemia	Massachusetts, USA	Some statistically significant dose-response trends were found.
(Hattchouel, Laplanche, and Hill 1996)	16 km	Cancer mortality	France	No excess cancer mortality in the population aged 0 to 64 years residing around French nuclear sites.
(Siffel, Otos, and Czeizel 1996)	30 km	Congenital abnormalities and germinal mutations	Hungary	The slightly elevated radiation background (0.20.4 mu Sv/year) due to the operation of the nuclear plant studied does not affect germinal and somatic mutations in children.
(Viel, Richardson, and Danel 1993)	35 km	Childhood leukemia	French	This nonsignificant finding is compatible with no increased risk and also with a sevenfold excess risk. Therefore, it reinforces the necessity of conducting a case-control survey
(Prindull, Demuth, and Wehinger 1993)	25 km	Neoplastic disease	Germany	Children living in the vicinity of this nuclear power plant do not have an increased risk of developing neoplastic disease.

Table 2.5-Continued

Studies	Distance thresholds of residential proximity to nuclear power plant (NPP) or Nuclear facility (NF)	Health outcomes	Regions	Conclusions
(Michaelis et al. 1992)	5 km, 15 km	Childhood malignancies	Germany	Increased risk ratio in subgroups for acute leukemia before five years of age and for lymphomas.
(Hatch and Wallenstein 1991)	10 mile	Cancer rates	USA	Radiation emissions did not account for the observed increase of odds ratio.

significant increase in cancer risk when compared with other children (Kaatsch et al. 2008; Spix et al. 2008). However, the results have raised a debate among researchers. Some studies supported the association between the childhood cancer and residential proximity to nuclear facilities (Baker and Hoel 2007; Brender, Maantay, and Chakraborty 2011; Fairlie 2009, 2010; Morris and Knorr 1996). Others found no statistically significant evidence of increased childhood cancer risk near nuclear facilities (Davis et al. 2006; McLaughlin and Clarke 1993; McLaughlin et al. 1993; Sharp et al. 1996; Spycher et al. 2011). Therefore, the nuclear facility-childhood cancer association is still an open question (Ghirga 2010). Besides childhood cancer, other health outcomes near nuclear facilities have also been examined in the literature. The health outcomes include escalated sex odds (Bochud et al. 2012; Scherb, Kusmierz, and Voigt 2013; Scherb and Voigt 2011, 2009), chromosome aberrations in the inhabitants (Ilyinskikh et al. 2000), birth defects (Queisser-Luft et al. 2011), painful miscarriages (Akhir and Alamgir 2012), lung cancer (Brown et al. 2004), thyroid-nodules (Mettler et al. 1992), and circulatory system diseases (CSDs) (Canu et al. 2012).

However, few studies have examined the association between maternal residential proximity to nuclear facilities and LBW in offspring (the Nuclear Facilities-LBW association) (Table 3.1). Mangones, Visintainer, and Brumberg (2013) and Wang et al.(2010) found that LBW was not related to residential proximity to nuclear facilities in their study areas. Slama et al. (2008) concluded that there was no increased risk of low birth weight in the "canton" (electoral ward) with nuclear facilities when compared with reference areas in France. However, most of these studies were outside of the United States (Slama et al. 2008; Wang et al. 2010), and only one used a U.S. study population

(Mangones, Visintainer, and Brumberg 2013). The only U.S.-based study (Mangones, Visintainer, and Brumberg 2013) focused on five Hudson Valley counties in New York state near a nuclear reactor. To the best of our knowledge, no study has investigated the Nuclear Facilities-LBW association in the southern United States. Moreover, previous studies had limited study areas and used much smaller study population sizes when compared with this dissertation research.

2.3.3. Analysis Method

Most the published studies investigating health outcomes near nuclear facilities used the "proximity-based method" for exposure assessment. The proximity-based method categorizes people near nuclear facilities into different groups based on their residential distances to nuclear facilities using certain distance thresholds.

Various distance thresholds have been used in studies of associations between residential proximity to nuclear facilities and health outcomes (Table 3.1). The frequencies of these thresholds are illustrated in Figure 2.4. The range of thresholds is from 5 kilometers to 50 kilometers (Figure 2.4). Because the common assumption behind many studies was that higher risk would exist in places closer to nuclear facilities, most studies used comparatively small distance thresholds. The Nuclear Facilities-LBW association might be sensitive to zones delineated by different distance thresholds. However, most of the published studies only used one set of predefined distance thresholds in the model and failed to investigate the influence of different distance thresholds on analysis results.

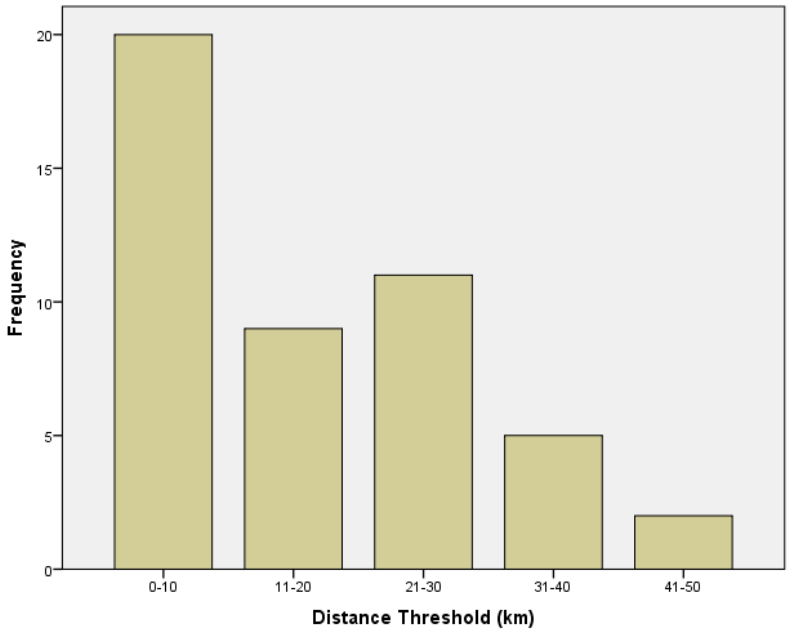

Figure 2.4 Distance thresholds of residential proximity to nuclear facilities used in health outcome research

2.4. Limitation in Environmental Risk Factor for LBW Research

A growing body of literature has included birth weight as a research topic, especially during the last decade. The topic has raised research interests of scientists from all over the world. The research of environmental risk factors for low birth weight has been an important part of the literature. After reviewing the literature on environmental risk factors, including ambient air pollution and nuclear facilities, this research has found following limitations.

2.4.1. Limitations in the Ambient Air Pollution-LBW Association Research

2.4.1.1. Types of Ambient Air Pollutants

In previous studies, two categories of ambient air pollutants have been examined as potential environmental risk factors for LBW. A large number of studies have linked LBW with exposure to the "CAPs and related pollutants (parameters)," while much less

research has focused on the "other air pollutants (parameters)." Therefore, a large gap existed between the publication quantities of the two categories. Only a few chemicals in the second category have been investigated, but there were many other chemicals in this category that could possibly have adverse effect on LBW, such as the TRI chemicals and TCEQ chemicals. These chemicals have not been thoroughly investigated as environmental risk factors for LBW.

2.4.1.2. Exposure Windows

Existing studies have used various exposure windows to examine the AAP-LBW association, which made it difficult to reach a consistent conclusion. A standardized protocol for critical exposure window exploration was absent in the literature.

Although over twenty different exposure windows have been used among published works, the time durations and starting times of those exposure windows were very limited. Limited choices of exposure windows might have restricted the exploration of more critical exposure windows with more flexible time durations and starting times. For each study, the exposure windows were usually predefined before the analysis and inflexible during the study. Therefore, prior knowledge about starting times and time durations of critical exposure windows was required if researchers wanted to accurately include the critical exposure windows in the predefinition, which was not always possible. A good solution to this limitation would be using flexible exposure windows in the analysis. However, no existing research has used this method to explore the association between maternal exposure to air pollution and low birth weight in offspring.

Moreover, most studies have only considered the maternal exposure after conception. The exposure windows before conception have been seldom included in the analysis of AAP-LBW association.

2.4.2. Limitations in the Nuclear Facilities-LBW Association Research

Many studies have investigated different health outcomes near nuclear facilities using statistical analysis. However, only very few studies have examined the association between maternal residential proximity to the nuclear facilities and LBW in offspring. To the best of our knowledge, no study has investigated the Nuclear Facilities-LBW association in the southern United States. Moreover, previous studies had limited study areas and used much smaller study population sizes when compared with this dissertation research.

Most of the published studies on the Nuclear Facilities-LBW association have used the "proximity-based method" to conduct epidemiological analysis. The key parameters of this method were the distance thresholds. However, these studies only used one set of predefined distance thresholds in the model and failed to investigate the sensitivity of the Nuclear Facilities-LBW association to zones delineated by different distance thresholds.

3. DATA SOURCES AND METHODOLOGY

3.1. Study Area

The study area of this dissertation was the state of Texas, United States. There are several reasons why Texas was chosen for this dissertation research. First, Texas has the largest area in the 48 contiguous United States. Second, Texas is the second most populous states in United States, with a total population of 25,145,561 in 2010 (U.S. Census Bureau 2015). Third, it has racially/ethnically diverse population, among which 45.3% (n = 11,397,345) were non-Hispanic whites, 11.5% (n = 2,886,825) were non-Hispanic blacks, 37.6% (n = 9,460,921) were Hispanics, 0.7% (n = 170,972) were Native Americans, and 3.8% (n = 964,596) were Asians (U.S. Census Bureau 2010).

3.2. Data Sources

This dissertation used two types of data, including environmental data and birth data. The environmental data consisted of three parts: air emission data, air quality monitoring data, and nuclear facility data.

3.2.1. Environmental Data

3.2.1.1. Air Emission Data

The air emission data were collected from the United States Environmental Protection Agency (U.S. EPA) Toxic Release Inventory (TRI) program. The TRI program is a mandatory program established by Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) to support and promote emergency planning and to provide the public with information about releases of toxic chemicals in

their community (U.S. EPA 2013a). The TRI program requires U.S. facilities in different industry sectors to report annually the information about their location, chemicals released, and estimated release amount into various environmental media, such as air and water bodies. Currently, more than 650 air pollutants have been covered in the online TRI database (U.S. EPA 2013a) .

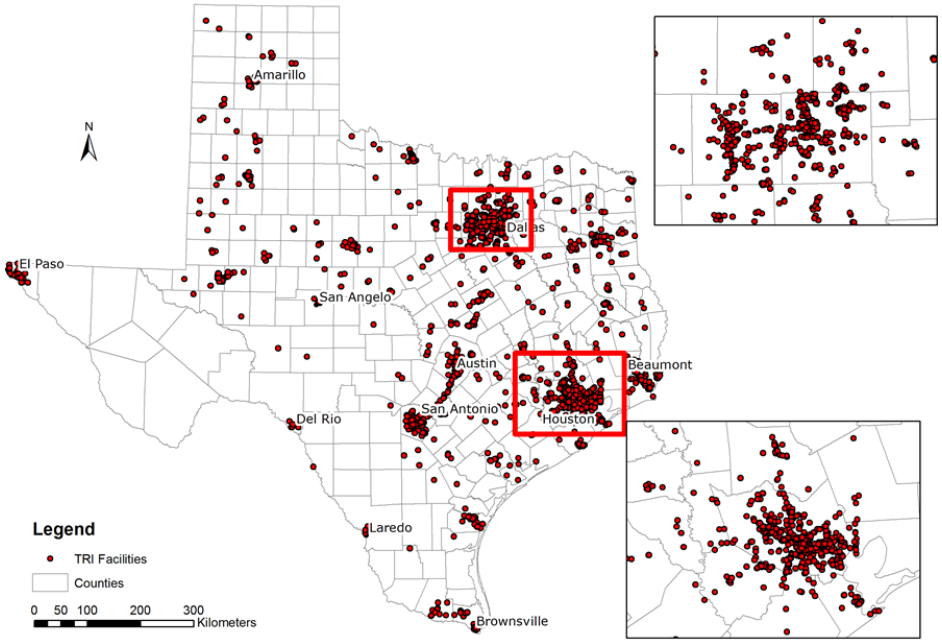

Figure 3.1 Geocoded Toxic Release Inventory (TRI) facilities in Texas during 1996-2008

This dissertation only extracted data in Texas during 1996-2008 from the online TRI database. During the thirteen years, a total of 449 chemicals have been released into the air by the industrial facilities in Texas. In each year, over 1,400 industrial facilities reported air emissions to TRI program. This dissertation geocoded the available facility addresses in the TRI databases in three steps using multiple geocoding methods. The details of the geocoding process is provided in Brender et al. (2014). On average, 89.66%

of the TRI facilities were successfully geocoded during the 13-year period (Figure 3.1). More details of the TRI data can be found in the EPA project report (Zhan et al. 2015).

3.2.1.2. Air Quality Monitoring Data

The air quality monitoring data were obtained from the Texas Commission on Environmental Quality (TCEQ). The data represented the ground truth, and were used as the "gold standard" at a given location to evaluate the validity of estimated exposure intensities from other exposure assessment models at that location. During the last 40 years, the TCEQ has collected air quality data and associated information from over 250 ambient monitoring sites in Texas (TCEQ 2014). The air quality monitoring data were maintained in the Texas Air Monitoring Information System (TAMIS) database for downloading. Each record in the database contained 393 variables measuring different air parameters, including criteria air pollutants (CAPs), hazardous air pollutants (HAPs), volatile organic compounds (VOC's), and meteorological data. Among the variables, a total of 367 were ambient concentrations of air pollutants monitored using different samplers. These samplers included canister samplers, carbonyl samplers, and $PM_{2.5}$ samplers, et al. (TCEQ 2013). This study selected the monitoring sites that were active during 1996-2008. During the 13-year period, a total of 331 monitoring sites had reported data to the TAMIS database. The locations of these monitoring sites were geocoded as shown in Figure 3.2. These monitoring sites were not evenly distributed in Texas. Most of the monitoring sites were located in urban areas, and concentrated in the Houston, Dallas, El Paso, and Beaumont areas.

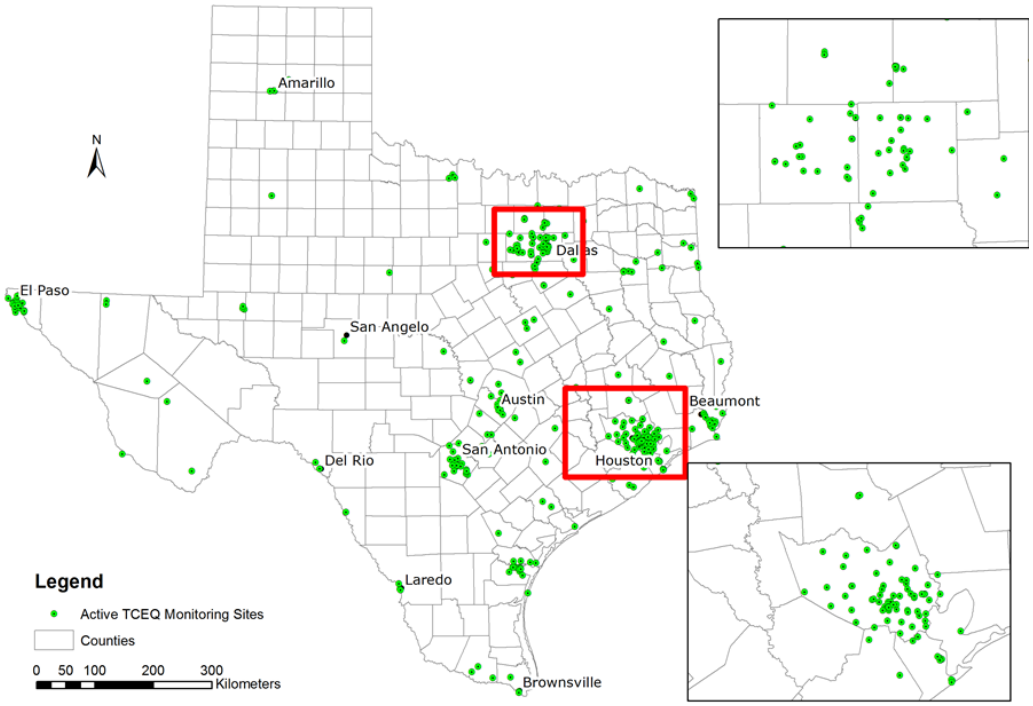

Figure 3.2 Active Texas Commission on Environmental Quality (TCEQ) air quality monitoring sites in Texas during 1996-2008

3.2.1.3. Nuclear Facility Data

The nuclear facility data were collected from United States Nuclear Regulatory Commission (U.S. NRC). Figure 3.3 shows the distribution of the 100 operating commercial nuclear power reactors that generate electricity in the United States in 2015 (U.S. NRC 2015a). All of them were regulated by the U.S. NRC. This research extracted the nuclear facilities in operation during 1996-2008 in Texas. There were two nuclear plants with four units selected (Table 3.1).

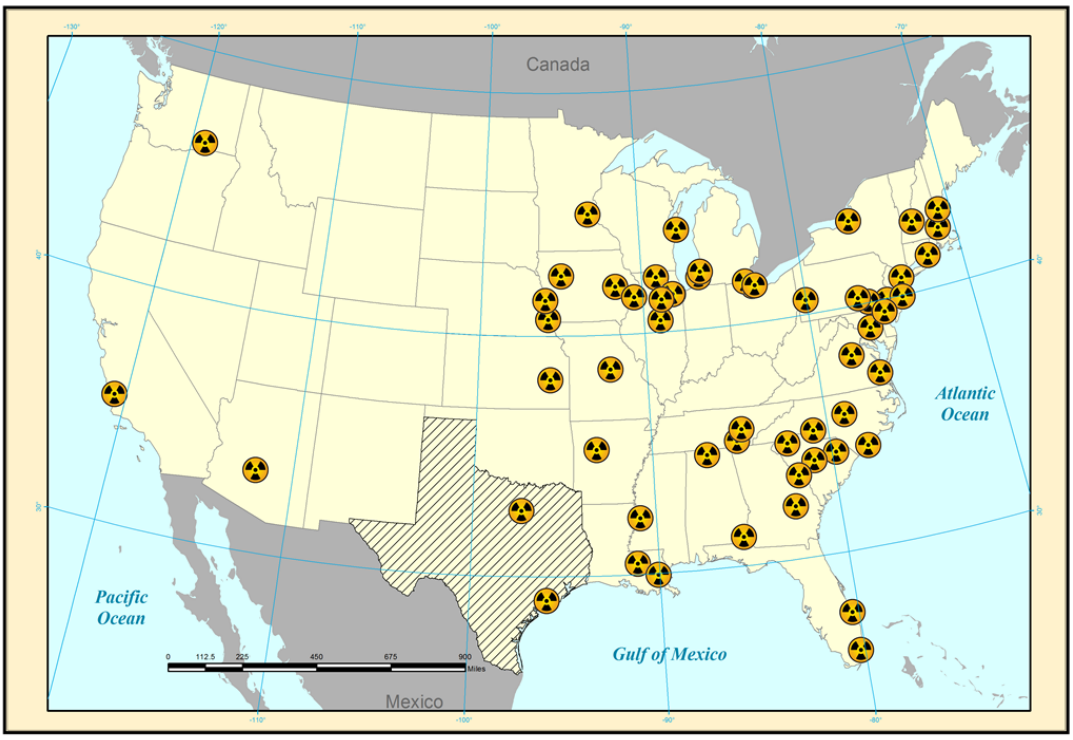

Figure 3.3 Operating commercial nuclear power reactors that generate electricity in the United States in 2015 (Study area Texas shaded)

Table 3.1 Information about nuclear power plants in Texas during 1996-2008

Plant Name	Location	Unit Number	Reactor Type	Containment Type	Licensee	Operating License Issued	Operating License Expires
South Texas Project	Bay City, TX (90 MI SW of Houston, TX)	South Texas Project, Unit 1	Pressurized Water Reactor	Dry, Ambient Pressure	STP Nuclear Operating Co.	3/22/1988	8/20/2027
		South Texas Project, Unit 2	Pressurized Water Reactor	Dry, Ambient Pressure	STP Nuclear Operating Co.	3/28/1989	12/15/2028
Comanche Peak Steam Electric Station	Glen Rose, TX (40 MI SW of Fort Worth, TX)	Comanche Peak Steam Electric Station, Unit 1	Pressurized Water Reactor	Dry, Ambient Pressure	Luminant Generation Co., LLC	4/17/1990	2/8/2030
		Comanche Peak Steam Electric Station, Unit 2	Pressurized Water Reactor	Dry, Ambient Pressure	Luminant Generation Co., LLC	4/6/1993	2/2/2033

3.2.2. Birth Data

Birth certificate data were obtained from the Center for Health Statistics in the Texas Department of State Health Services (TX DSHS) for all registered births in Texas from 1996 to 2008. Each birth certificate record included the following variables: geocoded coordinates of maternal residential address at delivery; birth location; birth weight; year of birth; plurality; child's sex; prenatal care; mother's characteristics (age at delivery, race/ethnicity, education, marital status, gestational age in weeks, date for last menstrual period (LMP); and tobacco use during pregnancy); and father's characteristics (age, race/ethnicity, and education). The dissertation excluded births with incomplete location information, plural delivery, weight less than 1,000 grams or greater than 5,500 grams, invalid date for LMP, or gestational age greater than 44 weeks or less than 32 weeks. This dissertation also omitted births occurred outside of Texas and births to non-Texas residents. Then, LBW cases in this dissertation were births who had birth weights of less than 2,500 grams, and were delivered between 1996 and 2008 (n = 94,106); controls were births with weights of greater than or equal to 2,500 grams during the 13-year period (n = 3,386,971).

3.3. Protection of Human Subjects

Texas DSHS Institutional Review Board (IRB) has approved the use and analyses of the birth data in this dissertation. The IRB review involved an agreement between Texas DSHS and data users to ensure the confidentiality of the human subjects. According to the agreement, the following provisions were required during the processing and analyses of the birth data.

a) The birth data are treated as strictly confidential.

b) During the study, the data are maintained in a password-protected computer in secure networks with up-to-date firewall and security software. A cabinet with access limited only to the data users is used to lock up the computer when not in use. Any hardcopy data that might allow identification of families (e.g. printouts to check quality issues or spot maps) are kept in the locked cabinet as well.

c) The presentation and publication of results may not include specific individual case/control information or make any case/control identifiable.

d) The confidential dataset will be destroyed one year after the research is finished. A non-confidential dataset will be created and maintained.

3.4. Methodology Overview

This dissertation consists of three studies. I call them the TRI Chemicals-LBW association study, the TCEQ Chemicals-LBW association study, and the Nuclear Facilities-LBW association study, respectively. The first study (the TRI Chemicals-LBW association study) examined the association between maternal exposure to TRI chemicals and LBW in offspring in Texas. It employed spatial analysis and geocomputational methods to assess maternal exposure to TRI chemicals, developed statistical procedures to identify TRI chemicals that were most likely to be associated with LBW, and used a case-control epidemiological study design to validate the association between the identified chemicals and LBW. The second study (the TCEQ Chemicals-LBW association study) examined the association between maternal exposure to TCEQ chemicals and LBW in offspring. This study employed spatio-temporal analysis method to estimate maternal exposure to TCEQ chemicals, developed statistical procedures to identify TCEQ chemicals and corresponding critical exposure windows that were most

likely to be associated with LBW in offspring. The third part (the Nuclear Facilities-LBW association study) examined association between maternal residential proximity to nuclear facilities and LBW in offspring in Texas. It used a case-control study design together with the proximity-based model to investigate the Nuclear Facilities-LBW association, and then conducted sensitivity analysis on distance thresholds of the proximity-based model to further validate the results.

4. THE TRI CHEMICALS-LBW ASSOCIATION STUDY

4.1. Introduction

Clean air is vitally important for human health. With increasing awareness about the adverse health effects associated with air pollution (Bobak and Leon 1999; Darrow, Klein, Strickland, et al. 2011; Polichetti et al. 2013; Srám et al. 2005), the general public is always concerned about how air pollutants in the living environment may affect human health. LBW, as an important predictor of infants' health, is one of the human health outcomes that may be associated with certain environmental risk factors (Ebisu, Belanger, and Bell 2008). To address public concerns about the risk, environmental epidemiological analysis is usually used to examine whether or not maternal exposure to certain air pollutants is associated with LBW in offspring.

Chemicals released into the air from Toxic Release Inventory facilities (TRI chemicals) belong to the "other air pollutants" category (Table 2.2), which may have adverse effects on birth weight of infants (Aguilera et al. 2009; Gladen et al. 2000; Slama et al. 2009). However, as noted in Chapter 2, TRI chemicals did not receive enough attention in previous research when compared to criteria air pollutants (CAPs). Only a small portion of TRI chemicals has been investigated in studies related to birth weight. Therefore, this chapter attempted to identify any associations between maternal exposure to TRI chemicals and LBW in offspring based on the analysis of massive georeferenced data.

The study discussed in this chapter intends to answer research question 1 elaborated in Chapter 1. The remainder of this chapter is organized as follows. Section

4.2 provides a detailed description of the data and methodology. The results of TRI Chemical-LBW associations are presented in Section 4.3. Finally, Section 4.4 wraps up the chapter with a discussion of the results and a presentation of the conclusions.

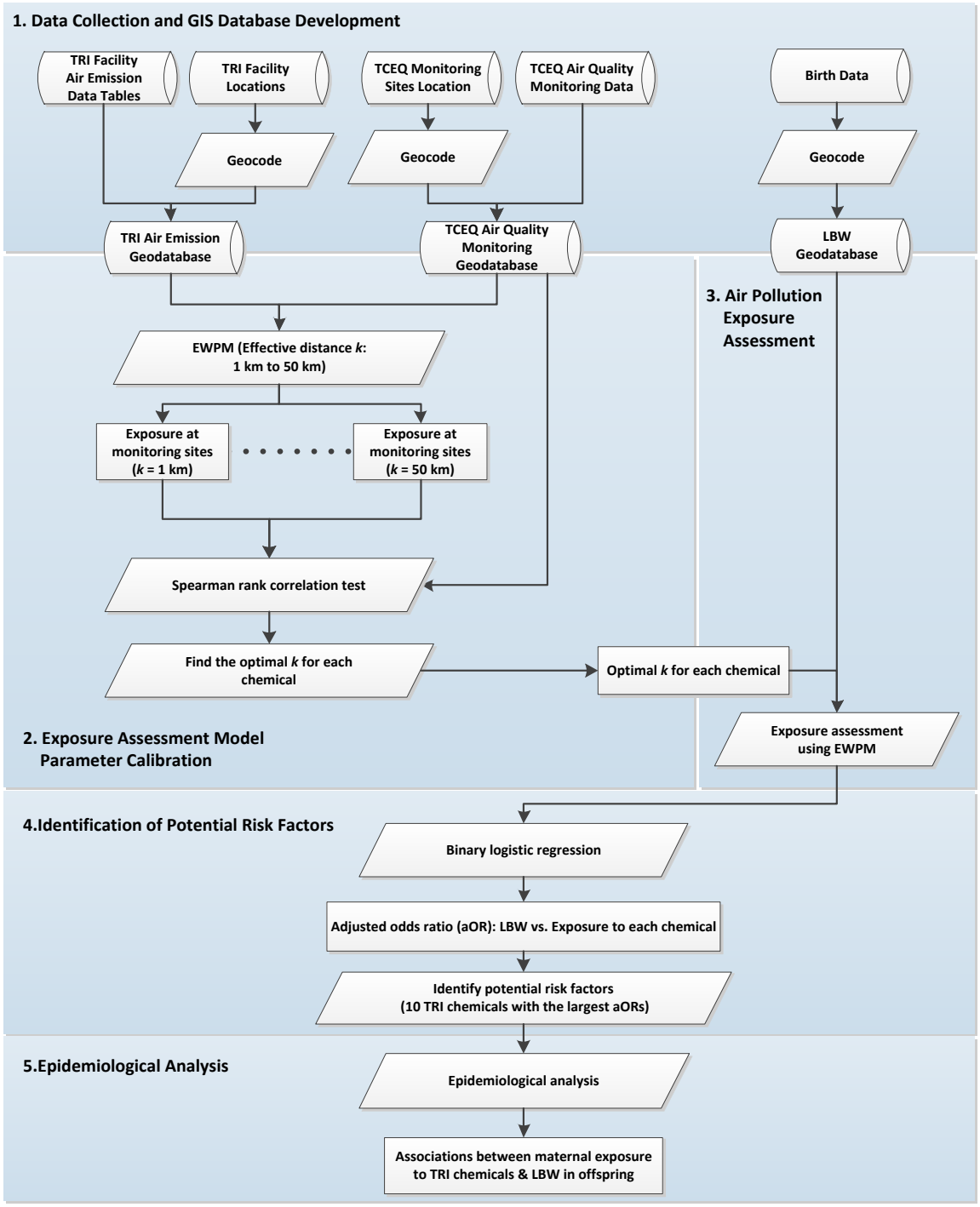

Figure 4.1 Framework of methodology: The TRI Chemicals-LBW association study

4.2. Data and Methodology

This study employed spatial analysis and geocomputational methods to assess maternal exposure to TRI chemicals, developed statistical procedures to identify TRI chemicals that are most likely to be associated with LBW in offspring, and used a case-control epidemiological study design to validate the identified TRI Chemical-LBW association. The methodology framework consisted of five steps as shown in Figure 4.1.

4.2.1. Data Collection and GIS Database Development

The analyses of this study involved three datasets, including birth data, air emission data, and air quality monitoring data. Details about the three datasets are descripted below.

4.2.1.1. Birth Data

Birth certificate data were obtained from the Center for Health Statistics in the Texas Department of State Health Services. This study selected the birth certificates based on the criteria and procedure described in Section 3.2.2. LBW cases were births who had birth weights of less than 2,500 grams, and were delivered between 1996 and 2008 (n = 94,106). Then the study randomly selected controls from the birth certificate data. These control-births were frequency matched to cases by year of birth. This study selected four controls for each case to ensure enough study power. Each birth certificate record included the following variables: geocoded coordinates of maternal residential address at delivery; birth location; birth weight; year of birth; plurality; child's sex; prenatal care; mother's characteristics (age at delivery, race/ethnicity, education, marital status, gestational age in weeks, date for last menstrual period; and tobacco use during

pregnancy); and father's characteristics (age, race/ethnicity, and education). Last, this study constructed a LBW geodatabase containing the georeferenced locations of cases and controls, as well as non-spatial variables obtained from the birth certificates.

4.2.1.2. Air Emission Data

Air emission data were obtained from the U.S. Environmental Protection Agency (U.S. EPA) Toxic Release Inventory (TRI) program and geocoded based on procedures described in Section 3.2.1.1. This study developed a TRI air emission geodatabase containing both spatial and non-spatial data of TRI facilities. The spatial data were the geographic locations of TRI facilities in Texas from 1996 to 2008 obtained through geocoding (Figure 3.1). The non-spatial data involved tables that summarized the yearly air emission amount of 449 TRI chemicals from these industrial facilities during 1996-2008.

4.2.1.3. Air Quality Monitoring Data

The air quality monitoring data have been obtained from the Texas Commission on Environmental Quality (TCEQ) and pre-processed using the procedure described in Section 3.2.1.2. This study constructed an air quality monitoring geodatabase to encapsulate both spatial and non-spatial data about the TCEQ air quality monitors. The spatial data were the geographic locations of active monitoring sites in Texas during 1996-2008 obtained through geocoding (Figure 3.2). The non-spatial data were monitoring records in Texas during 1996-2008 derived from the Texas Air Monitoring Information System (TAMIS) database. The monitoring records provided observations of

24-hour integrated ambient concentrations of 367 air pollutants sampled every three or six days (TCEQ 2015).

4.2.2. Exposure Assessment Model Parameter Calibration

This study used a modified version of the EWPM (Zou et al. 2009b) to estimate exposure intensities at a location to a given air pollutant from several emission sources within a given distance. The formula for calculating the exposure intensity to air pollutant θ for a person at a residence location i is given by Equation (4.1) below.

$$A^{\theta}{}_{i} = \sum_{j=1}^{m} E^{\theta}{}_{ij} \times T^{\theta}{}_{ij} \times ((k^{\theta} - D_{ij}) / k^{\theta}), \text{ for } (D_{ij} \le k^{\theta}) \quad (4.1)$$

In this equation, $A^{\theta}{}_{i}$ is the estimated exposure intensity of a person at location i to air pollutant θ, represented by the quantity of air pollutant θ reaching location i from all emission sources (j, $j=1, 2, \ldots\ldots, m$); $E^{\theta}{}_{ij}$ and $T^{\theta}{}_{ij}$ are the emission rate and duration of emission of air pollutant θ from emission source j relative to location i; D_{ij} is the distance between location i and location of emission source j; m is the number of emission sources relevant to a person at location i in the area in question; k^{θ} is the effective distance beyond which air pollutant θ is considered to have no harm to an individual (Zou et al. 2009b). This model uses the term (k^{θ} - D_{ij})/ k^{θ} to replace the term (1/ D_{ij}) in the original EWPM (Zou et al. 2009b). This replacement can avoid an overestimation of exposure intensities in the original EWPM when the distance (D_{ij}) is very short. This study retained the acronym "EWPM" to represent this modified version of the model.

In the EWPM model, the effective distance *k* is assumed to be related to chemical properties and meteorological parameters. It is difficult to define the optimal effective distance for each chemical. This research utilized a geocomputational method to calibrate the parameter (effective distance *k*). For each chemical, this study utilized the following steps to determine its optimal effective distance (*k*). First, given different effective distances from 1 km to 50 km with a 1 km increment at each iteration, this study repeatedly estimated the exposure intensities at the locations of the TCEQ monitors using EWPM for 50 times. Therefore, a total of 50 different exposure intensity datasets were created for each chemical. Second, the 50 estimated exposure intensities datasets were paired with the monitoring data to calculate the Spearman rank correlation coefficients. In the third and final step, through a comparison of the 50 correlation coefficients, this study determined each chemical's optimal effective distance (*k*) corresponding to the maximum positive correlation between the estimated exposure intensity and monitored data for the chemical in question.

Table 4.1 Basic information about the estimated exposure intensity data and the air quality monitoring data

Dataset	Type	Data Processing	Measurement Unit	Spatial Resolution	Temporal Resolution
The estimated exposure intensity data	Model estimates	EWPM[1] + TRI[2]	lb	Street address level	Annual
The air quality monitoring data	Monitoring (observed) data	From TCEQ TAMIS database[3]	ppbv[4]	Street address level (only locations of monitoring sites)	Aggregated form "24 hour integrated" to "annual average"

[1] Emission Weighted Proximity Model (EWPM)
[2] Toxic Release Inventory (TRI)
[3] Texas Commission on Environmental Quality (TCEQ) Texas Air Monitoring Information System (TAMIS) database.
[4] Parts per billion by volume (ppbv)

It is important to make two observations about the parameter calibration process. First, because the estimated exposure intensity data were annual level estimates, the same monitor in different years were considered as different monitor samples. Second, the original air quality monitoring data provided observations of 24-hour integrated ambient concentrations of each air pollutant sampled every three or six days. However, the estimated exposure intensities data are annual level estimates for each air pollutant (Table 4.1). To make the values corresponding to the same air pollutant from the two datasets comparable, this study calculated the annual average concentration of each air pollutant at each monitoring site based on the original air quality monitoring data (Table 4.1).

4.2.3. Air Pollution Exposure Assessment

In this step, this study used the modified EWPM again to estimate exposure intensities to TRI chemicals at the maternal residential locations of LBW cases and controls. The effective distance (k) in the modified EWPM for each chemical was the optimal effective distance obtained based on the procedure described in Section 4.2.2. The input data for the model were the LBW geodatabase and TRI air emission geodatabase.

4.2.4. Identification of Potential Risk Factors

This study used odds ratio (OR) to identify the chemicals that are most likely to be the risk factors. First, the estimated maternal exposure intensity values to a given chemical were only categorized into two groups (zero and greater than zero) for screening purposes. Then this study calculated the odds ratio (OR) of LBW in offspring by maternal exposure intensities groups (zero and greater than zero) for each TRI

chemical using the binary logistic regression. The zero-exposure-intensity group was considered as the reference group for all analyses. Odds ratios were adjusted for potential confounding variables that may be associated with the LBW.

The potential confounding variables were selected based on suggestions from the literature (e.g. child's sex, gestational weeks, maternal age, education, and race/ethnicity). Then this study applied a linear regression model with birth weight as a continuous dependent variable and all potential confounding variables (excluding air pollution variables) as independent variables to explore whether expected associations were observed (e.g., maternal age associated with lower birth weight). Only the variables exhibiting statistically significant associations with birth weight were incorporated into the binary logistic regression model to calculate the adjusted odds ratios (aORs) representing the TRI Chemical-LBW associations.

Based on the aORs, this study selected the TRI chemicals which were most likely to be associated with LBW in offspring. These TRI chemicals were then used for subsequent epidemiological analysis.

4.2.5. Epidemiological Analysis

For each identified TRI chemical, estimated exposure intensity values were categorized into four levels (exposure intensities at zero and greater than zero divided into three equal groups) based on the control-mothers distribution of values. Then this study used a binary logistic regression to validate the associations (OR and 95% confidence interval (CI)) between maternal exposure to these TRI chemicals and LBW in offspring. The zero-exposure-intensity group served as the reference group for all

analyses. In this step, the ORs were adjusted for the same confounding variables as described in Section 4.2.4.

4.3. Results

4.3.1. Demographic Characteristics

This study selected a total of 94,106 LBW cases and 376,424 controls that were frequency matched to cases by year of birth. Table 4.2 shows a comparison of cases and controls by child's sex, mother's age at delivery, mother's race-ethnicity, gestational length, year of birth, public health region of maternal residence at the time of delivery, and mother's education. Female births had a higher percentage of LBW cases than male births among the study population. Compared with the control-mothers, case-mothers were more likely to be non-Hispanic black, or have younger delivery age, shorter gestational length, or less education.

4.3.2. Estimated Exposure Intensities

In order to calibrate the effective distance (k) as mentioned in Section 4.2.2, this study need to find the shared chemicals between the air emission data and air quality monitoring data. In total, the two datasets shared 78 chemicals (Appendix A). After calibrating the effective distance (k) for each chemical, this study only selected chemicals for which the estimated exposure intensities and the monitoring intensities were significantly positively correlated (correlation coefficient greater than zero and p-value less than 0.05). Therefore, a total of 40 chemicals with correlation coefficients ranging from 0.107 to 0.754 were selected (Table 4.3). Table 4.3 also listed the optimal effective distances (k) and sample sizes of the 40 chemicals. As mentioned in Section 4.2.2, the

data of the same monitor in different years were considered as different monitoring samples. Therefore, sample sizes of the 40 chemicals ranged from 24 to 597 (Table 4.3).

Table 4.2 Selected characteristics of low birth weight cases and frequency-matched controls, Texas, 1996-2008

Characteristic		**Cases (n = 94,106)**		**Controls (n = 376,424)**		**Total (n = 470,530)**	
		n	**%**	**n**	**%**	**n**	**%**
Child's sex	Male	39,787	42.3	192,170	51.1	231,957	49.3
	Female	54,319	57.7	184,254	48.9	238,573	50.7
Mother's age at delivery (years)	11-19	18,791	20.0	51,840	13.8	70,631	15.0
	20-24	28,850	30.7	104,253	27.7	133,103	28.3
	25-29	22,139	23.5	103,103	27.4	125,242	26.6
	30-34	14,898	15.8	76,662	20.4	91,560	19.5
	35-39	7,470	7.9	34,021	9.0	41,491	8.8
	>40	1,957	2.1	6,543	1.7	8,500	1.8
	Unknown	1	<0.1	2	<0.1	3	<0.1
Mother's race/ethnicity	Non-Hispanic White	27,642	29.4	142,220	37.8	169,862	36.1
	Non-Hispanic black	18,344	19.5	39,968	10.6	58,312	12.4
	Hispanic	43,366	46.1	179,051	47.6	222,417	47.3
	Others, non-Hispanic	4,754	5.1	15,185	4.0	19,939	4.2
Gestational length (weeks)	37	29,089	30.9	39,432	10.5	68,521	14.6
	38	25,426	27.0	83,900	22.3	109,326	23.2
	39	18,488	19.6	107,832	28.6	126,320	26.8
	40	10,578	11.2	80,679	21.4	91,257	19.4
	41	5,307	5.6	38,516	10.2	43,823	9.3
	42	2,830	3.0	14,717	3.9	17,547	3.7
	43	1,634	1.7	7,805	2.1	9,439	2.0
	44	754	.8	3,543	.9	4,297	.9
Year of birth	1996	5,739	6.1	22,956	6.1	28,695	6.1
	1997	5,750	6.1	23,000	6.1	28,750	6.1
	1998	5,910	6.3	23,640	6.3	29,550	6.3
	1999	5,974	6.3	23,896	6.3	29,870	6.3
	2000	6,333	6.7	25,332	6.7	31,665	6.7
	2001	6,433	6.8	25,732	6.8	32,165	6.8
	2002	7,023	7.5	28,092	7.5	35,115	7.5
	2003	7,166	7.6	28,664	7.6	35,830	7.6
	2004	7,535	8.0	30,140	8.0	37,675	8.0
	2005	8,451	9.0	33,804	9.0	42,255	9.0
	2006	9,071	9.6	36,284	9.6	45,355	9.6
	2007	9,236	9.8	36,944	9.8	46,180	9.8
	2008	9,485	10.1	37,940	10.1	47,425	10.1

Table 4.2-Continued

Characteristic		Cases (n = 94,106)		Controls (n = 376,424)		Total (n = 470,530)	
		n	%	n	%	n	%
Public health service region	1	3,855	4.1	11,866	3.2	15,721	3.3
	2	1,992	2.1	7,692	2.0	9,684	2.1
	3	24,253	25.8	106,683	28.3	130,936	27.8
	4	3,230	3.4	11,551	3.1	14,781	3.1
	5	2,561	2.7	8,306	2.2	10,867	2.3
	6	23,094	24.5	93,920	25.0	117,014	24.9
	7	9,236	9.8	41,031	10.9	50,267	10.7
	8	10,324	11.0	37,836	10.1	48,160	10.2
	9	2,565	2.7	8,306	2.2	10,871	2.3
	10	4,183	4.4	14,944	4.0	19,127	4.1
	11	8,813	9.4	34,289	9.1	43,102	9.2
Education	< High School	33,963	36.1	113,301	30.1	147,264	31.3
	High School	30,200	32.1	108,392	28.8	138,592	29.5
	> High School	29,082	30.9	151,886	40.3	180,968	38.5
	Unknown	861	0.9	2,845	0.8	3,706	0.8

Based on the optimal effective distances (*k*) (Table 4.3), this study estimated intensities of exposure to the 40 chemicals at the maternal residence locations of LBW cases and controls. As an example, Figure 4.2 displays the distribution of estimated exposure intensities in Texas during 1996-2008 for chemical Propylene (CAS number 115071). The exposure intensity maps were produced based on the following steps. First, the study extracted the centroids of 4,388 census tracts in Texas, which were considered as the virtual point receptors to air pollution exposure. The underlying assumption was that the estimated exposure intensity at a census tract's centroid was used to represent the exposure intensity of that census tract. Second, EWPM was used to estimate the average exposure intensities of each chemical at the 4,388 census tract's centroids. Third, the study categorized census tracts into seven groups based on their intensity values of exposure to a given chemical. The census tracts without exposure (estimated exposure intensity equaled to zero) were put into the first group; other census tracts were

categorized into six groups based on an equal-interval classification of exposure intensity values.

Table 4.3 Calibrated parameters (effective distance *k* in EWPM) for selected chemicals

Pollutants	CAS Number[a]	Sample Size	Spearman Rank Correlation Test		
			Optimal *k* (km)	Coefficient[b]	P-value (2-tailed)
Zinc (fume or dust)	7440666	24	7	0.754	<0.001
Propylene	115071	561	50	0.739	<0.001
Methyl tert-butyl ether	1634044	559	40	0.721	<0.001
1,3-butadiene	106990	597	33	0.671	<0.001
Ethylene	74851	561	50	0.653	<0.001
Cyclohexane	110827	597	6	0.629	<0.001
Arsenic	7440382	50	6	0.605	<0.001
Cadmium	7440439	24	7	0.561	0.004
Styrene	100425	597	10	0.555	<0.001
Naphthalene	91203	34	20	0.552	<0.001
Acrolein	107028	35	14	0.527	0.001
Chlorobenzene	108907	597	13	0.523	<0.001
N-hexane	110543	597	12	0.519	<0.001
Chloroform	67663	597	42	0.508	<0.001
Vinyl chloride	75014	597	11	0.508	<0.001
1,2-dichloroethane	107062	597	14	0.493	<0.001
Benzene	71432	597	12	0.490	<0.001
Dichloromethane	75092	597	16	0.442	<0.001
Chlorine	7782505	153	48	0.437	<0.001
Cumene	98828	597	16	0.437	<0.001
Chloromethane	74873	300	17	0.379	<0.001
Butyraldehyde	123728	151	44	0.348	<0.001
Ethylbenzene	100414	597	12	0.315	<0.001
1,2-dichloropropane	78875	597	4	0.266	<0.001
Carbon tetrachloride	56235	596	15	0.263	<0.001
Trichloroethylene	79016	597	17	0.244	<0.001
Benzo(g,h,i)perylene	191242	69	10	0.242	0.046
Toluene	108883	597	13	0.236	<0.001
Tetrachloroethylene	127184	597	41	0.234	<0.001
Mercury	7439976	153	50	0.191	0.018
Methyl isobutyl ketone	108101	253	3	0.186	0.003
1,2,4-trimethylbenzene	95636	597	3	0.182	<0.001

Table 4.3-Continued

Pollutants	CAS Number[a]	Sample Size	Spearman Rank Correlation Test		
			Optimal *k* (km)	Coefficient[b]	P-value (2-tailed)
Bromine	7726956	153	45	0.178	0.027
O-xylene	95476	597	10	0.164	<0.001
1,1,2-trichloroethane	79005	597	6	0.160	<0.001
Isobutyraldehyde	78842	253	49	0.158	0.012
Lead	7439921	182	1	0.157	0.034
Vinylidene chloride	75354	597	14	0.155	<0.001
1,1,2,2-tetrachloroethane	79345	435	50	0.154	0.001
1,1,1-trichloroethane	71556	592	50	0.107	0.009

[a] A unique numerical identifier assigned by Chemical Abstracts Service (CAS) to every chemical substance described in the open scientific literature.
[b] Sorted by descending Spearman rank correlation coefficients.

The patterns of propylene exposure intensities remained relatively stable during the 13-year period. High exposure levels were observed in the southeastern coastal area of Texas. The northeastern area and western corner of Texas had sparse areas with mid-level intensity. In southeastern Texas, the Beaumont area had the highest exposure intensity level, but the intensity level decreased as year went by. The Houston area had a high exposure intensity level consistently during the 13 years. Starting from year 2002, the northern corner of Texas began to have a low level of exposure intensities.

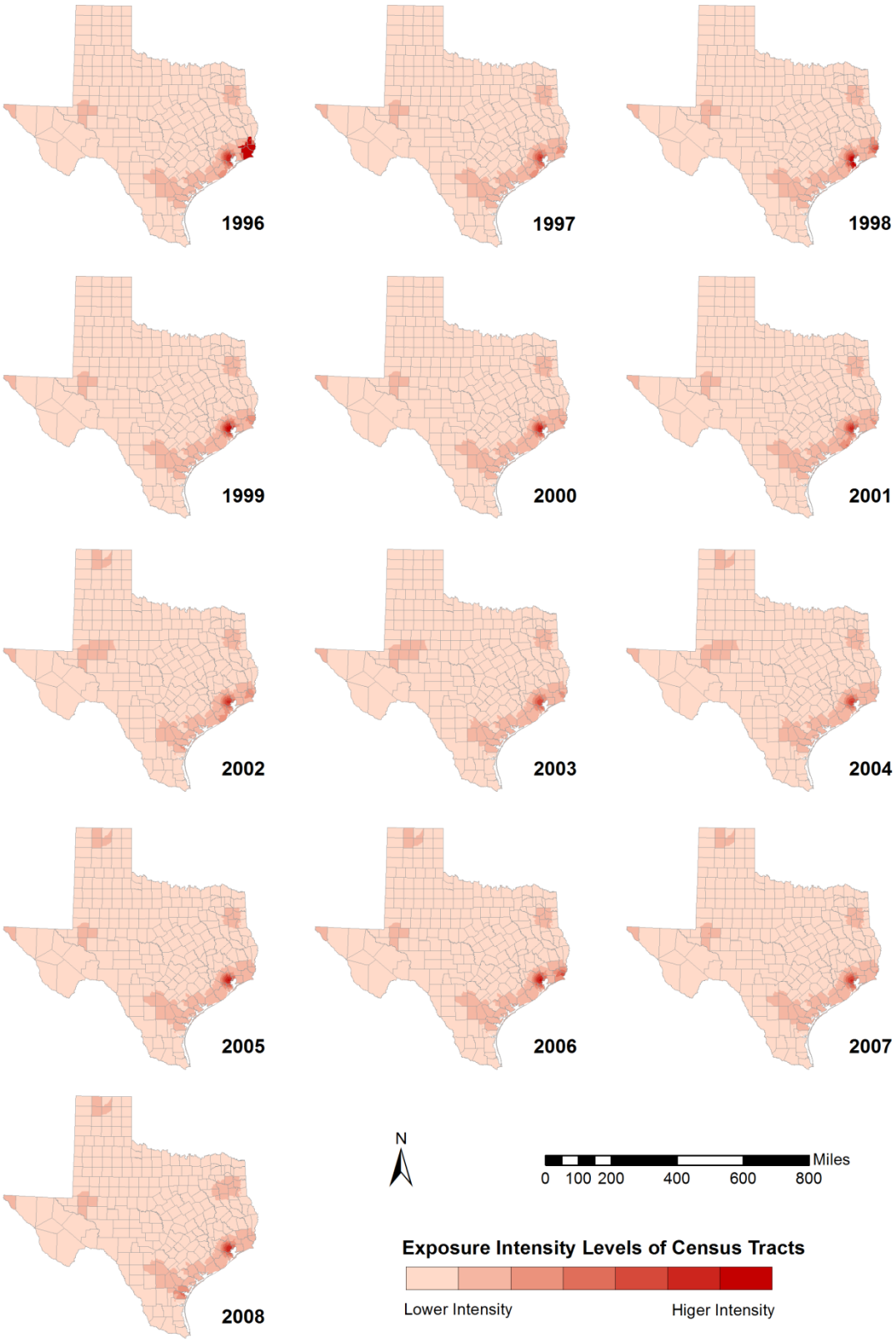

Figure 4.2 Distribution of estimated propylene exposure intensities, Texas, 1996-2008

4.3.3. Identified Potential Risk Factors

Table 4.4 Difference in birth weight associated with selected non-pollution variables (95% confidence interval)

Variable	Difference in birth weight (g)	
Child's Sex		
Male (reference)		
Female	-148.5	(-151.7 to -145.3)
Mother's race/ethnicity		
Non-Hispanic White (reference)		
Non-Hispanic Black	-233.6	(-239.0 to -228.3)
Hispanic	-37.8	(-41.6 to -33.9)
Others, non-Hispanic	-212.5	(-220.8 to -204.3)
Mother's education		
High School (reference)		
< High School	-22.5	(-26.8 to -18.3)
> High School	62.2	(58.1 to 66.4)
Mother's age (years)		
30-34 (reference)		
11-19	-182.8	(-188.7 to -176.9)
20-24	-107.8	(-112.7 to -103.0)
25-29	-36.6	(-41.4 to -31.8)
35-39	-2.0	(-8.5 to 4.4)
>39	-61.4	(-73.8 to -49.0)
Gestational length (weeks)		
40 (reference)		
37	-517.4	(-522.9 to -511.9)
38	-264.3	(-269.3 to -259.5)
39	-101.8	(-106.6 to -97.1)
41	26.3	(20.0 to 32.7)
42	-52.2	(-61.3 to -43.2)
43	-78.1	(-90.0 to -66.3)
44	-76.7	(-93.8 to -59.7)

Table 4.4 shows results from the linear regression model using birth weight as a continuous dependent variable and all potential confounding variables (excluding air pollution variables) as independent variables. Statistically significant associations were noted between all variables and birth weights. Specifically, female infants tended to have

lower birth weights than male infants. Mothers with shorter gestational length, less education, or younger age were associated with lower birth weights in offspring. Moreover, when compared with non-Hispanic White mothers, mothers from other race/ethnicity groups had infants with lower birth weights. Therefore, the ORs for the association between maternal TRI chemical exposure and LBW in offspring need to be adjusted for child's sex, maternal race/ethnicity, age, education, and gestational length. Because of the uneven distribution of births in both time and space (Table 4.2), the ORs were also adjusted for the year of birth and public health region of maternal residence.

Table 4.5 shows the odds ratios of LBW in offspring for different maternal exposure intensity groups (zero and greater than zero) corresponding to the 40 TRI chemicals after adjusting for confounding variables. Using the two-group categorization for exposure intensities, 26 chemicals showed statistically significant adjusted odds ratios (aORs), which indicated elevated risks of LBW in exposed groups than in the non-exposed reference groups. The increased risk ranged from 3% to 11% (aOR: 1.03 - 1.11). From these 26 chemicals, this study selected ten chemicals with the largest aOR values as the potential risk factors for LBW. The ten chemicals were methyl isobutyl ketone (aOR 1.06, 95% CI 1.02, 1.10), cyclohexane (aOR 1.06, 95% CI 1.03, 1.08), zinc (fume or dust) (aOR 1.11, 95% CI 1.07, 1.14), styrene (aOR 1.06, 95% CI 1.04, 1.08), o-xylene (aOR 1.06, 95% CI 1.03, 1.10), n-hexane (aOR 1.06, 95% CI 1.05, 1.08), benzene (aOR 1.07, 95% CI 1.05, 1.09), cumene (aOR 1.05, 95% CI 1.04, 1.07), propylene (aOR 1.07, 95% CI 1.04, 1.11), and ethylene (aOR 1.06, 95% CI 1.03, 1.09).

Table 4.5 Maternal exposure intensities to selected chemicals and low birth weight in offspring, Texas, 1996-2008

Pollutant (CAS Number)	Exposure intensity[a]	Cases		Controls		Adjusted OR[b] (95% CI)
		n	%	n	%	
Lead (7439921)	0	93,566	99.4	374,437	99.5	1.00 (Referent)
	>0	539	0.6	1,985	0.5	1.08 (0.97,1.19)
Methyl isobutyl ketone (108101)	0	90,527	96.2	363,251	96.5	1.00 (Referent)
	>0	3,578	3.8	13,171	3.5	1.06 (1.02,1.10)
1,2,4-trimethylbenzene (95636)	0	87,878	93.4	353,982	94	1.00 (Referent)
	>0	6,227	6.6	22,440	6	1.04 (1.01,1.08)
1,2-dichloropropane (78875)	0	94,039	99.9	376,109	99.9	1.00 (Referent)
	>0	66	0.1	313	0.1	0.90 (0.68,1.19)
Cyclohexane (110827)	0	83,643	88.9	338,958	90	1.00 (Referent)
	>0	10,462	11.1	37,464	10	1.06 (1.03,1.08)
Arsenic (7440382)	0	93,417	99.3	373,061	99.1	1.00 (Referent)
	>0	688	0.7	3,361	0.9	0.87 (0.80,0.95)
1,1,2-trichloroethane (79005)	0	93,820	99.7	375,099	99.6	1.00 (Referent)
	>0	285	0.3	1,323	0.4	0.94 (0.82,1.07)
Cadmium (7440439)	0	93,904	99.8	375,675	99.8	1.00 (Referent)
	>0	201	0.2	747	0.2	1.00 (0.85,1.18)
Zinc (fume or dust) (7440666)	0	88,293	93.8	355,507	94.4	1.00 (Referent)
	>0	5,812	6.2	20,915	5.6	1.11 (1.07,1.14)
Benzo(g,h,i)perylene (191242)	0	81,549	86.7	330,263	87.7	1.00 (Referent)
	>0	12,556	13.3	46,159	12.3	1.05 (1.03,1.08)
Styrene (100425)	0	49,818	52.9	207,156	55	1.00 (Referent)
	>0	44,287	47.1	169,266	45	1.06 (1.04,1.08)
O-xylene (95476)	0	87,570	93.1	351,576	93.4	1.00 (Referent)
	>0	6,535	6.9	24,846	6.6	1.06 (1.03,1.10)
Vinyl chloride (75014)	0	91,483	97.2	365,684	97.1	1.00 (Referent)
	>0	2,622	2.8	10,738	2.9	1.01 (0.96,1.06)
N-hexane (110543)	0	49,395	52.5	207,821	55.2	1.00 (Referent)
	>0	44,710	47.5	168,601	44.8	1.06 (1.05,1.08)
Benzene (71432)	0	57,515	61.1	241,393	64.1	1.00 (Referent)
	>0	36,590	38.9	135,029	35.9	1.07 (1.05,1.09)
Ethylbenzene (100414)	0	46,323	49.2	193,485	51.4	1.00 (Referent)
	>0	47,782	50.8	182,937	48.6	1.05 (1.03,1.07)
Chlorobenzene (108907)	0	90,701	96.4	362,535	96.3	1.00 (Referent)
	>0	3,404	3.6	13,887	3.7	1.03 (0.99,1.08)

Table 4.5-Continued

Pollutant (CAS Number)	Exposure intensity[a]	Cases		Controls		Adjusted OR[b] (95% CI)
		n	%	n	%	
Toluene (108883)	0	34,431	36.6	144,272	38.3	1.00 (Referent)
	>0	59,674	63.4	232,150	61.7	1.04 (1.03,1.06)
Acrolein (107028)	0	89,771	95.4	358,969	95.4	1.00 (Referent)
	>0	4,334	4.6	17,453	4.6	0.99 (0.95,1.03)
1,2-dichloroethane (107062)	0	88,823	94.4	355,851	94.5	1.00 (Referent)
	>0	5,282	5.6	20,571	5.5	1.04 (1.01,1.08)
Vinylidene chloride (75354)	0	92,058	97.8	367,925	97.7	1.00 (Referent)
	>0	2,047	2.2	8,497	2.3	1.01 (0.96,1.07)
Carbon tetrachloride (56235)	0	89,175	94.8	357,608	95	1.00 (Referent)
	>0	4,930	5.2	18,814	5	1.03 (1.00,1.07)
Dichloromethane (75092)	0	65,993	70.1	264,645	70.3	1.00 (Referent)
	>0	28,112	29.9	111,777	29.7	1.05 (1.03,1.07)
Cumene (98828)	0	61,985	65.9	252,556	67.1	1.00 (Referent)
	>0	32,120	34.1	123,866	32.9	1.05 (1.04,1.07)
Chloromethane (74873)	0	86,596	92	346,944	92.2	1.00 (Referent)
	>0	7,509	8	29,478	7.8	1.01 (0.98,1.04)
Trichloroethylene (79016)	0	73,728	78.3	292,487	77.7	1.00 (Referent)
	>0	20,377	21.7	83,935	22.3	1.02 (0.99,1.04)
Naphthalene (91203)	0	40,672	43.2	166,439	44.2	1.00 (Referent)
	>0	53,433	56.8	209,983	55.8	1.03 (1.01,1.05)
1,3-butadiene (106990)	0	65,644	69.8	268,719	71.4	1.00 (Referent)
	>0	28,461	30.2	107,703	28.6	1.04 (1.01,1.06)
Methyl tert-butyl ether (1634044)	0	38,766	41.2	154,842	41.1	1.00 (Referent)
	>0	55,339	58.8	221,580	58.9	1.01 (0.99,1.03)
Tetrachloroethylene (127184)	0	49,584	52.7	190,574	50.6	1.00 (Referent)
	>0	44,521	47.3	185,848	49.4	1.00 (0.98,1.03)
Chloroform (67663)	0	76,756	81.6	310,105	82.4	1.00 (Referent)
	>0	17,349	18.4	66,317	17.6	1.05 (1.02,1.08)
Butyraldehyde (123728)	0	75,170	79.9	303,338	80.6	1.00 (Referent)
	>0	18,935	20.1	73,084	19.4	1.04 (1.01,1.07)
Bromine (7726956)	0	86,118	91.5	344,955	91.6	1.00 (Referent)
	>0	7,987	8.5	31,467	8.4	1.04 (1.01,1.08)
Chlorine (7782505)	0	45,278	48.1	178,119	47.3	1.00 (Referent)
	>0	48,827	51.9	198,303	52.7	1.00 (0.98,1.02)
Isobutyraldehyde (78842)	0	75,604	80.3	303,983	80.8	1.00 (Referent)
	>0	18,501	19.7	72,439	19.2	1.04 (1.01,1.07)

Table 4.5-Continued

Pollutant (CAS Number)	Exposure intensity[a]	Cases		Controls		Adjusted OR[b] (95% CI)
		n	%	n	%	
1,1,2,2-tetrachloroethane (79345)	0	82,712	87.9	332,492	88.3	1.00 (Referent)
	>0	11,393	12.1	43,930	11.7	1.04 (1.01,1.07)
1,1,1-trichloroethane (71556)	0	69,804	74.2	278,371	74	1.00 (Referent)
	>0	24,301	25.8	98,051	26	1.03 (1.00,1.06)
Mercury (7439976)	0	56,512	60.1	230,924	61.3	1.00 (Referent)
	>0	37,593	39.9	145,498	38.7	1.04 (1.02,1.06)
Propylene (115071)	0	60,915	64.7	250,086	66.4	1.00 (Referent)
	>0	33,190	35.3	126,336	33.6	1.07 (1.04,1.11)
Ethylene (74851)	0	62,595	66.5	256,209	68.1	1.00 (Referent)
	>0	31,510	33.5	120,213	31.9	1.06 (1.03,1.09)

[a]Exposure intensity value based on maternal residential proximity to source(s) of air emissions and estimated pounds of chemical emitted annually.
[b]Adjusted for birth year, public health region, child's sex, maternal race/ethnicity, age, education, and gestational length.

4.3.4. Results of Epidemiological Analysis

For each of the ten identified chemicals, this study categorized the exposure intensities into four levels (zero and greater than zero divided into three equal groups) based on the control-mother's distribution of values. Table 4.6 shows the associations between maternal exposure to the ten chemicals and LBW in offspring. All chemicals showed statistically significant associations with LBW. However, the associations tended to be weak with the aORs ranging from 1.03 to 1.14. The strongest association was noted with Zinc (fume and dust) (aOR in the second quartile: 1.14, 95% CI 1.08, 1.20), which indicated that mothers in the second quartile of zinc exposure intensity had 14% higher risk of delivering LBW babies when compared with mothers in the reference group. Out of the ten chemicals, four chemicals showed statistically significant aORs in all three exposed groups (low, medium, high). Those four chemicals are styrene, n-hexane, benzene, and cumene. Six other chemicals showed statistically significant aORs in two

exposed groups, including methyl isobutyl ketone, cyclohexane, zinc (fume or dust), o-xylene, propylene, and ethylene. For each of the ten chemicals, mothers with exposure intensities in the fourth quartile had statistically significant elevated risk of LBW in offspring when compared with those in the respective reference group.

Table 4.6 Maternal exposure intensities to selected chemicals (with top ten aORs in Table 4.5) and low birth weight in offspring, Texas, 1996-2008

Pollutant (CAS Number)	Exposure intensity[a]	Cases		Controls		Adjusted OR[b] (95% CI)
		n	%	n	%	
Methyl isobutyl ketone (108101)	0	90,527	96.2	363,251	96.5	1.00 (Referent)
	0.01-50.40	1,119	1.2	4,391	1.2	0.98 (0.91,1.05)
	50.41-391.42	1,237	1.3	4,389	1.2	1.10 (1.03,1.18)
	>391.42	1,222	1.3	4,391	1.2	1.09 (1.01,1.16)
Cyclohexane (110827)	0	83,643	88.9	338,958	90.0	1.00 (Referent)
	0.01-88.41	3,669	3.9	12,489	3.3	1.08 (1.04,1.13)
	88.42-1,000.28	3,410	3.6	12,486	3.3	1.03 (0.98,1.07)
	>1,000.28	3,383	3.6	12,489	3.3	1.05 (1.01,1.10)
Zinc (fume or dust) (7440666)	0	88,293	93.8	355,507	94.4	1.00 (Referent)
	0.01-2.50	2,039	2.2	6,972	1.9	1.14 (1.08,1.20)
	2.51-77.74	1,959	2.1	6,971	1.9	1.13 (1.07,1.19)
	>77.74	1,814	1.9	6,972	1.9	1.05 (1.00,1.11)
Styrene (100425)	0	49,818	52.9	207,156	55.0	1.00 (Referent)
	0.01-1,493.43	14,201	15.1	56,426	15.0	1.03 (1.01,1.06)
	1,493.44-8,899.67	14,820	15.7	56,415	15.0	1.06 (1.04,1.08)
	>8,899.67	15,266	16.2	56,425	15.0	1.09 (1.06,1.12)
O-xylene (95476)	0	87,570	93.1	351,576	93.4	1.00 (Referent)
	0.01-482.86	2,160	2.3	8,283	2.2	1.05 (0.99,1.10)
	482.87-4,293.19	2,145	2.3	8,280	2.2	1.06 (1.01,1.12)
	>4,293.19	2,230	2.4	8,283	2.2	1.07 (1.01,1.12)
N-hexane (110543)	0	49,395	52.5	207,821	55.2	1.00 (Referent)
	0.01-344.45	14,137	15.0	56,203	14.9	1.03 (1.01,1.06)
	344.46-1,823.74	14,888	15.8	56,195	14.9	1.08 (1.06,1.11)
	>1,823.74	15,685	16.7	56,203	14.9	1.09 (1.06,1.11)
Benzene (71432)	0	57,515	61.1	241,393	64.1	1.00 (Referent)
	0.01-101.78	11,736	12.5	45,012	12.0	1.06 (1.04,1.09)
	101.79-822.02	12,105	12.9	45,005	12.0	1.07 (1.04,1.09)
	>822.02	12,749	13.5	45,012	12.0	1.09 (1.06,1.11)

Table 4.6-Continued

Pollutant (CAS Number)	Exposure intensity[a]	Cases		Controls		Adjusted OR[b] (95% CI)
		n	%	n	%	
Cumene (98828)	0	61,985	65.9	252,556	67.1	1.00 (Referent)
	0.01-12.98	10,948	11.6	41,292	11.0	1.05 (1.03,1.08)
	12.99-155.82	10,536	11.2	41,283	11.0	1.06 (1.04,1.09)
	>155.82	10,636	11.3	41,291	11.0	1.04 (1.02,1.07)
Propylene (115071)	0	60,915	64.7	250,086	66.4	1.00 (Referent)
	0.01-63,587.48	10,710	11.4	42,114	11.2	1.05 (1.01,1.09)
	63,587.49-333,407.85	11,445	12.2	42,108	11.2	1.06 (1.02,1.10)
	>333,407.85	11,035	11.7	42,114	11.2	1.04 (0.99,1.10)
Ethylene (74851)	0	62,595	66.5	256,209	68.1	1.00 (Referent)
	0.01-70,048.84	9,958	10.6	40,073	10.6	1.04 (1.00,1.07)
	70,048.85-407,399.18	10,780	11.5	40,067	10.6	1.06 (1.01,1.10)
	>407,399.18	10,772	11.4	40,073	10.6	1.03 (0.98,1.08)

[a]Exposure intensity value based on maternal residential proximity to source(s) of air emissions and estimated pounds of chemical emitted annually.
[b]Adjusted for birth year, public health region, child's sex, maternal race/ethnicity, age, education, and gestational length.

Three different patterns of aOR trends can be noted from the results. First, monotonically increasing trends existed between LBW in offspring and exposure to four chemicals, including styrene (highest aOR in the fourth quartile: 1.09, 95% CI 1.06, 1.12), o-xylene (aOR in the fourth quartile: 1.07, 95% CI 1.01, 1.12), n-hexane (highest aOR in the fourth quartile: 1.09, 95% CI 1.06, 1.11), and benzene (highest aOR in the fourth quartile: 1.09, 95% CI 1.06, 1.11). All exposed groups of these four chemicals showed statistically significant aORs except for the second quartile for o-xylene. These monotonically increasing trends indicated that the risk of having LBW babies increased as the estimated exposure intensities increased. Second, for five chemicals (methyl isobutyl ketone, cyclohexane, cumene, ethylene, and propylene), the trends did not show a monotonic increase in that the highest odds ratios were noted in the second or third quartile instead of the fourth quartile. Third, for zinc (fume or dust), it was interesting to note that the aORs showed a monotonically decreasing trend in the three exposed groups.

Although all these three exposed groups had statistically significant higher risk of LBW (aOR > 1) than their reference group, the highest odds ratio was noted in the second quartile (aOR 1.14, 95% CI 1.08, 1.20).

4.4. Discussions and Conclusions

This large population-based study used a geocomputational method to assess maternal exposure to TRI chemicals and a case-control design to investigate the association between maternal exposure to TRI chemicals and LBW in offspring. The whole analysis was an example of data mining in which ten top chemicals that were most likely to be associated with LBW were selected from all of the 449 chemicals emitted into the air from TRI facilities in Texas from 1996 to 2008. These ten chemicals include styrene, n-hexane, benzene, cumene, methyl isobutyl ketone, cyclohexane, zinc (fume or dust), o-xylene, propylene, and ethylene. The study found that case-mothers were more likely than control-mothers to have a higher level of exposure to these ten chemicals, based on their residential locations and reported annual releases from industry facilities. The risk of LBW increased monotonically when the exposure to styrene, o-xylene, n-hexane, or benzene intensities increased.

Exposure to some of the ten chemicals mentioned above has been linked to LBW in offspring in other studies. In a Spanish study on birth cohorts of the INMA-INfancia y Medio Ambiente (Environment and Childhood)-Project, BTEX (benzene, toluene, ethyl benzene, and xylene) exposure for women with few outdoor activities was found to be associated with birth weight reductions in offspring (Aguilera et al. 2009). An estimated reduction of 77 g (95% CI 7-146 g) in birth weight was associated with an interquartile range increase in BTEX exposure. In the present study, exposure intensities to benzene

and o-xylene, which were included in BTEX, were also found to be associated with LBW in offspring. Compared with the reference group, the exposed group had an increased LBW risk ranging from 5% to 9%. This weak association was similar to that found in the Spanish study (Aguilera et al. 2009). In a study conducted in Los Angeles County, California, the authors found 1%-3% increased odds of term LBW per interquartile range increase in maternal exposure to benzene and o-xylenes in the third trimester (Ghosh et al. 2012). The low percentage of increased risk matched the results of the present study. Based on $PM_{2.5}$ filters collected in three Connecticut counties and one Massachusetts county from August 2000 through February 2004, Bell et al. (2010) found that an interquartile range increase in maternal exposure was associated with LBW in offspring for zinc (a 12% increase in risk), silicon (10%), elemental carbon (13%), aluminum (11%), nickel (11%), and vanadium (8%). The present study also found association between exposure to zinc and LBW in offspring with aORs of the three exposed groups ranging from 1.05 to 1.14. Katakura et al.(2001) did an animal experiment using Wistar rats and found that birth weight, litter size, and sex ratio exhibited no statistically significant effects of styrene exposure within the variation range studied. The result contradicts with the 3%-6% increase odds of LBW in offspring for mothers exposed to styrene in the present study.

Although there were reported studies about benzene, o-xylene, zinc, and styrene, the other six chemicals (n-hexane, cumene, methyl isobutyl ketone, cyclohexane, propylene, and ethylene) were not covered in the existing LBW literature. The present research was the first study to discover associations between maternal exposure to those six chemicals and LBW in offspring. These new findings of the TRI Chemical-LBW

associations created new opportunities for further epidemiological, biological, and toxicological studies.

As shown in Table 4.6, six chemicals (methyl isobutyl ketone, cyclohexane, zinc, cumene, propylene, and ethylene) did not exhibit monotonically increasing trend in their aORs with the increase in exposure intensities. Similar trends were noted in associations between chlorinated solvent exposures and birth defect in offspring in a study conducted in Texas (Brender et al. 2014). Although the highest odds ratios were not observed in the fourth quartiles (highest categories of exposed intensities) of the six chemicals mentioned above, one should not conclude that higher exposure intensities were associated with lower risk of LBW in offspring. One possible explanation of this finding was that the study only included birth certificate data for live births and did not use data for other pregnancy outcomes, such as fetal death or induced termination. Higher exposure intensities might cause severe birth weight reductions during some pregnancies and further result in fetal deaths or induced terminations. In this situation, these pregnancies were not included in the birth data of the present study. As a result, the odds ratio in the higher exposure intensity group would have been biased towards one.

From the perspective of methodology, this study used a proximity model (EWPM) to estimate exposure intensities to TRI chemicals. The advantages of the EWPM include its simplicity and significantly lower costs of implementation. However, like other proximity models, the EWPM may introduce some degree of exposure misclassifications as discussed in Chapter 2. In order to evaluate the validity of the estimated exposure intensities from the EWPM, a prior study was conducted to compare the estimated exposure and monitoring data of 27 non-criteria air pollutants at 48

monitoring sites in Texas in 2005. The results from that study suggested that EWPM was a valid approach in situations where epidemiological analysis requires both environmental data and health outcome data that cover a large geographic area over multiple years (Gong, et. al, 2015). The present study utilized a geocomputational method to further improve the model accuracy of EWPM. Figure 4.3 showed a comparison of spearman rank correlation between EWPM-estimated exposure intensities and monitoring data by different model parameters (effective distances). For the 40 chemicals shared between the air quality monitoring data and air emission data (Table 4.5), the correlation coefficients based on calibrated parameter values (optimal effective distances) were higher than or equal to the ones using the 10 km as fixed effective distance (Figure 4.3). Some chemicals even had negative coefficients when 10 km was used, which indicated exposure misclassifications in the estimated results. As a result, it is recommended that future studies calibrate model parameter (effective distance) before using EWPM for exposure assessment.

There are several limitations in this study. First, air emission sources in this study only included the stacks of TRI industrial facilities, which were point emission sources. In future research, the exposure modeling process should consider more emission source types to include linear sources, area sources, and mobile sources. The TRI air emission data are self-reported by the industry facilities and are based on pollution emission amount rather than pollutant concentrations. These characteristics of the TRI air emission data may also introduce uncertainties into the exposure intensities estimated using the EWPM. The TRI air emission data are annual level, which also restrict the exposure assessment in finer temporal scales.

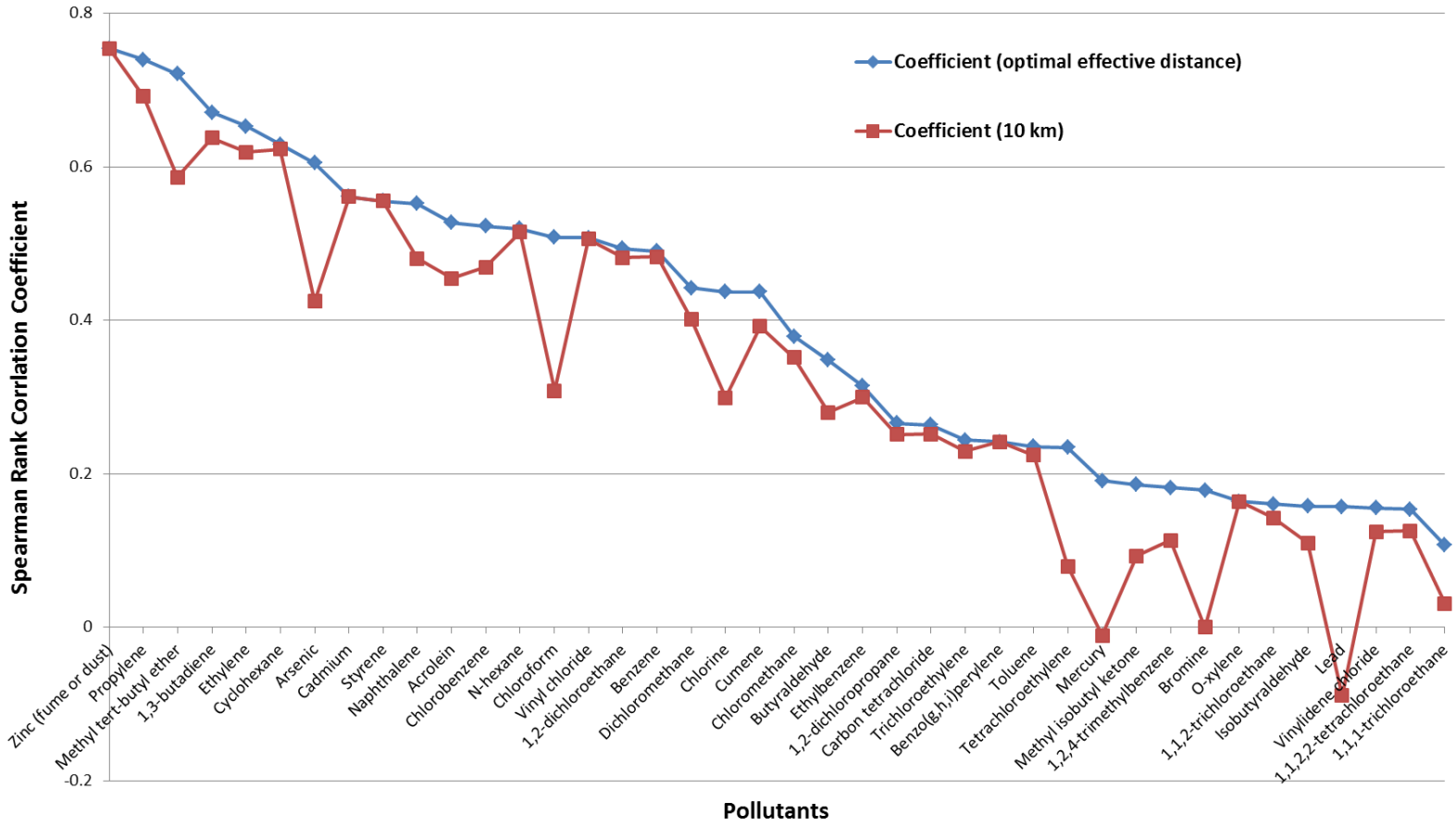

Figure 4.3 Correlation between EWPM-estimated exposure intensities and monitoring data by different model parameters (optimal effective distance vs. fixed effective distance)

Second, when estimating exposure intensities for mothers residing in areas bordering other states or Mexico, there may be edge effect because the emission sources outside Texas were not considered in this study. This situation may lead to underestimated exposure intensities for mothers living in these areas and introduce uncertainties to results of the epidemiological analysis. In the present study, only 8.92% (n = 41,957) of the total study population (both cases and controls) had maternal residence located within 10 km of the Texas border, and only 6.67% (n = 31,392) of the study population had maternal residence located 10-50 km to the Texas border. Therefore, the edge effect is limited in this study.

Third, since this study used monitoring sites as the sampling locations for exposure intensities to calibrate the EWPM parameters, the spatial distribution of the monitoring sites might also affect the results. Most monitoring sites were located in urban areas and concentrated in a few big cities, thus exposure intensities in suburban or rural areas were not well represented. One possible solution is to create evenly distributed sampling points by interpolating the existing monitoring values using the Kriging method. However, Whitworth et al. (2011) found that the Kriging method would introduce more uncertainties, which in turn affects the analysis results. As a result, additional studies are necessary to understand and mitigate the effect of geographic distribution of sampling points.

Fourth, this study assumed that maternal residential addresses were stable between conception and delivery. While it was true for most mothers, some mothers may change their residential locations during pregnancy (Canfield et al. 2006; Lupo et al. 2010) and the movement may cause exposure misclassifications for those mothers.

However, since the movement tended to be short distance movement, its effect in exposure assessment might be minimal (Lupo et al. 2010).

5. THE TCEQ CHEMICALS-LBW ASSOCIATION STUDY

5.1. Introduction

As noted in Chapter 2, LBW is an important predictor of infants' health (Ebisu, Belanger, and Bell 2008) and air pollution is considered as one of the environmental risk factors for LBW (Glinianaia et al. 2004; Maisonet et al. 2004; Ritz and Wilhelm 2008; Srám et al. 2005). However, in studies exploring associations between air pollution exposure and LBW, chemicals in the "other air pollutants" category (Table 2.2) have been investigated much less frequently than the criteria air pollutants (CAPs). A significant number of chemicals in the "other air pollutants" category have not been examined based on the literature. Because most of the 367 chemicals monitored by the TCEQ air quality monitoring sites (TCEQ chemicals) belonged to the "other air pollutants" category, this study intends to fill the gap in the literature through the TCEQ Chemicals-LBW association study.

The association between maternal air pollution exposure and LBW in offspring varied when different exposure time windows were used (Geer, Weedon, and Bell 2012; Morello-Frosch et al. 2010; Pearce et al. 2012). "Critical exposure windows" are limited temporal intervals during which maternal exposure to air pollutants may have the greatest potential to affect the birth weight in offspring. The general public were particularly concerned about the critical exposure windows. In reported studies, exposure windows were usually inflexible and were predefined before analysis using limited time durations and starting times. If no prior knowledge about starting times and time durations of critical exposure windows was provided, it would be difficult to include the real critical

exposure windows in the predefinition. Unlike previous studies, this study adopted flexible exposure windows to examine the air pollution-LBW associations. Additionally, few studies have considered exposure windows before conception in the exploration of air pollution-LBW associations. In order to fill the literature gap, this study included exposure windows before conception in the analysis. The TCEQ air quality monitoring data provided finer temporal resolution (every three or six days) than the air emission data used in Chapter 4 and thus were suitable for this study. This study attempted to create a standardized protocol for interactively exploring critical exposure windows of air pollution-LBW associations based on the analysis of massive georeferenced air quality monitoring data.

The study discussed in this chapter intends to answer research question 2 stated in Chapter 1. The remainder of this chapter is organized as follows. Section 5.2 provides a detailed description of the data and methodology. Section 5.3 reports the results of TCEQ Chemical-LBW associations. Section 5.4 wraps up the chapter with a discussion of the results and a presentation of the conclusions.

5.2. Data and Methodology

This study employed a spatio-temporal analysis method to estimate maternal exposure intensities to TCEQ chemicals, and developed statistical procedures to identify TCEQ chemicals and corresponding critical maternal exposure windows that were most likely to be associated with LBW in offspring. The methodology framework consisted of five steps as shown in Figure 5.1.

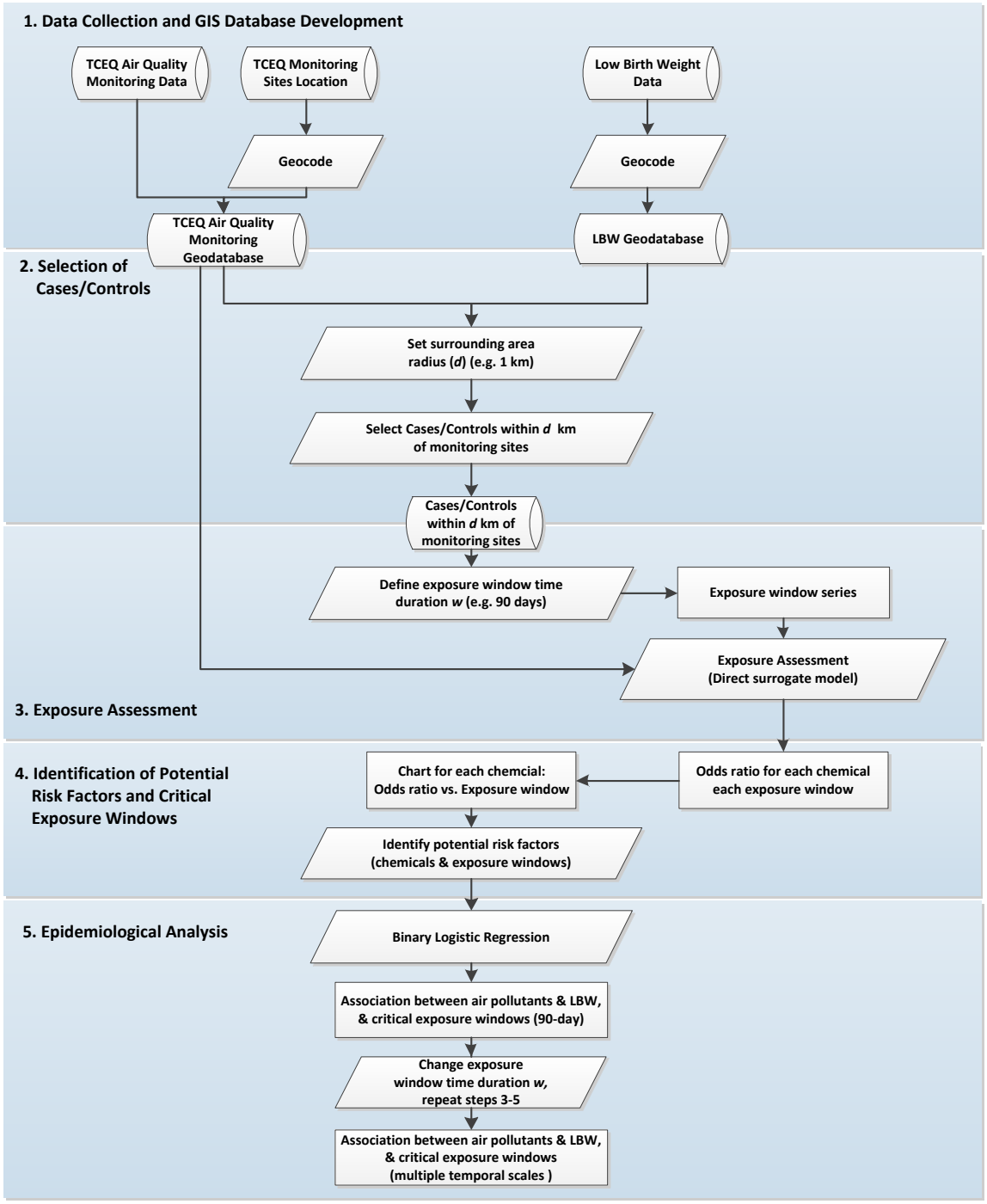

Figure 5.1 Framework of methodology: The TCEQ Chemicals-LBW association study

5.2.1. Data Collection and GIS Database Development

This study used air quality monitoring data and birth data. Details of the two datasets are descripted below.

5.2.1.1. Air Quality Monitoring Data

The original air quality monitoring records and the monitoring sites addresses were obtained from the Texas Commission on Environmental Quality (TCEQ) and pre-processed using procedures described in Section 3.2.1.2. An air quality monitoring geodatabase was created to include both spatial and non-spatial data of the air quality monitoring data. The spatial data were the geographic locations of active monitoring sites in Texas during 1996-2008 obtained through geocoding (Figure 3.2). The non-spatial data included monitoring records in Texas during 1996-2008 derived from the TAMIS database. The monitoring records provided observations of 24-hour integrated ambient concentrations of 367 air pollutants sampled every three or six days (TCEQ 2015).

Because air pollution samplers installed at each monitoring site were different and the activation/deactivation dates of each monitoring site varied, most monitoring sites only monitored a subset of the 367 chemicals within certain time periods. The ambient concentrations for chemicals or time periods that were not monitored were stored as missing values in the air quality monitoring geodatabase.

5.2.1.2. Birth Data

This study obtained birth certificate data from the Center for Health Statistics in the Texas Department of State Health Services. The birth certificates were selected based on the criteria and procedures described in Section 4.2.1.1. A total of 94,106 cases and

376,424 controls were used as the study population for further analysis. The controls were frequency matched to the cases by year of birth, After that, similar to what was described in Section 4.2.1.1, the georeferenced locations of the cases and controls, as well as other non-spatial variables obtained from the birth certificates were integrated into a LBW geodatabase.

5.2.2. Selection of Cases/Controls

This study used a direct surrogate model (Table 2.3) to estimate air pollution exposures. This model used data from ambient monitors as a surrogate for individual or community-level exposure to air pollutants (Bell 2006). In this model, concentrations of a given air pollutant were assumed to be spatially homogeneous in the area surrounding a given monitor. As mentioned in Section 2.2.3, the radius of the surrounding area (*d*) was an important parameter. Either too large or too small surrounding area would affect analysis results negatively. Therefore, this study set the surrounding area radius (*d*) to 1 km for analysis.

In order to estimate the exposure to a given chemical using the direct surrogate model, this study needs to select LBW cases and controls in areas surrounding the monitoring sites as follows. First, this study selected monitoring sites with records of that chemical during the study period. Then, LBW cases and controls within a given surrounding area radius (*d*) of these monitors were selected for further exposure assessment. Other LBW cases and controls were excluded from further analysis of that chemical because the required air quality monitoring data for exposure assessment were not available. The whole selection process was repeated for each given chemical. Figure 5.2 shows an example of the selection process. In this example, there are three

monitoring sites and sixteen LBW cases/controls. Monitoring site I has data records for both chemical A and B, while monitoring site II only has chemical A information and monitoring site III only has chemical B information. If the given chemical was A and the surrounding area radius (*d*) was 1 km, five LBW cases/controls (No. 3, 4, 13, 14, and 15) within 1 km of monitoring sites I and II would be selected, as shown in Figure 5.2.

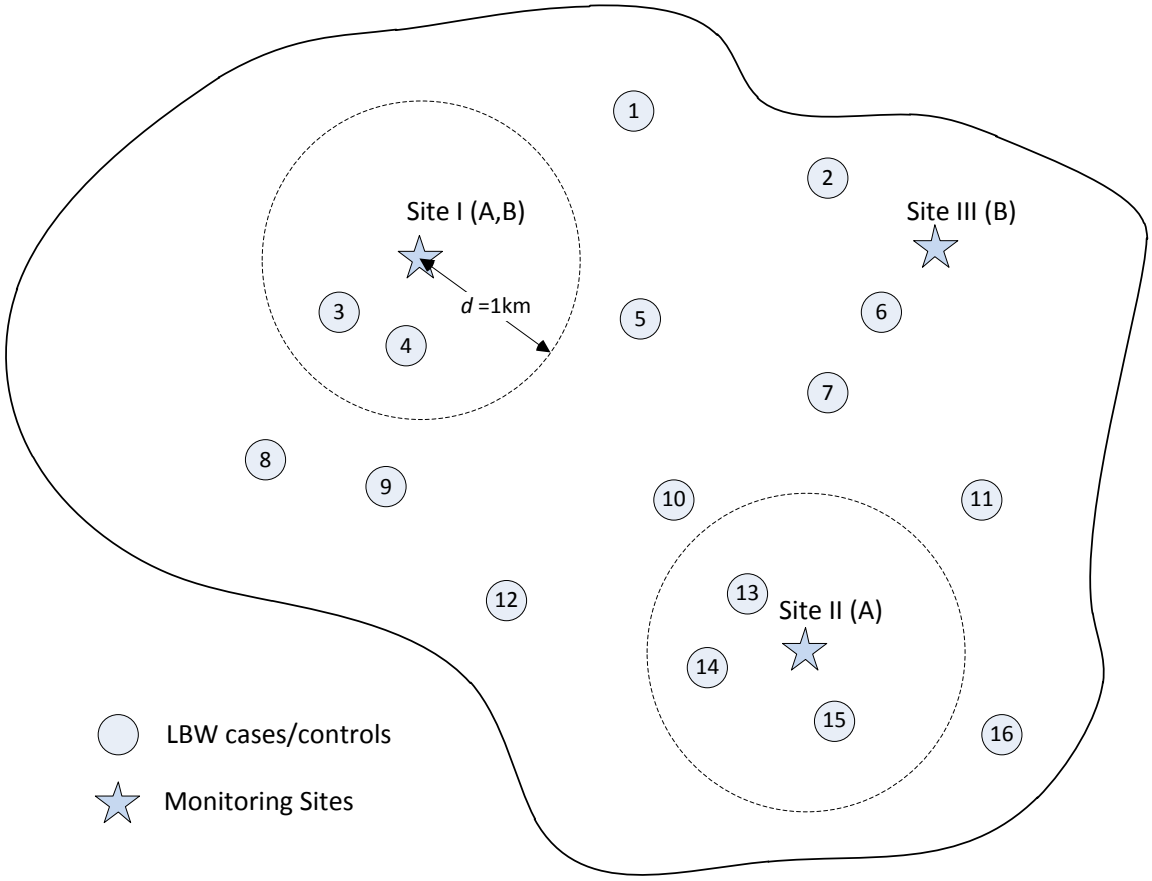

Figure 5.2 Selection of cases/controls based on a given chemical and a given surrounding area radius

5.2.3. Exposure Assessment

In this step, a time duration of exposure window (*w*) was defined first. This time duration (*w*) should be relatively large (e.g. 90 days) initially, because results associated with this initial exposure window time duration (*w*) were used for screening purpose. If any interesting results based on this time duration (*w*) were found, such as key chemicals

and critical exposure windows, the methods used in this study have the flexibility to refine the exposure window to a smaller time duration and perform the analysis at a finer temporal scale.

This study generated a series of exposure windows by sliding the exposure window from one year before conception to the day of birth with increments of 6 days at each step. As shown in Figure 5.3. Each rectangle represents an exposure window. The window series starts from the conception date minus 365 days, and a new window is added to the series by moving the window every 6 days to the right. This process is repeated until the entire study period is covered. The exact number of days in a window can be redefined as necessary. An example time window of 90 days is shown in Figure 5.3.

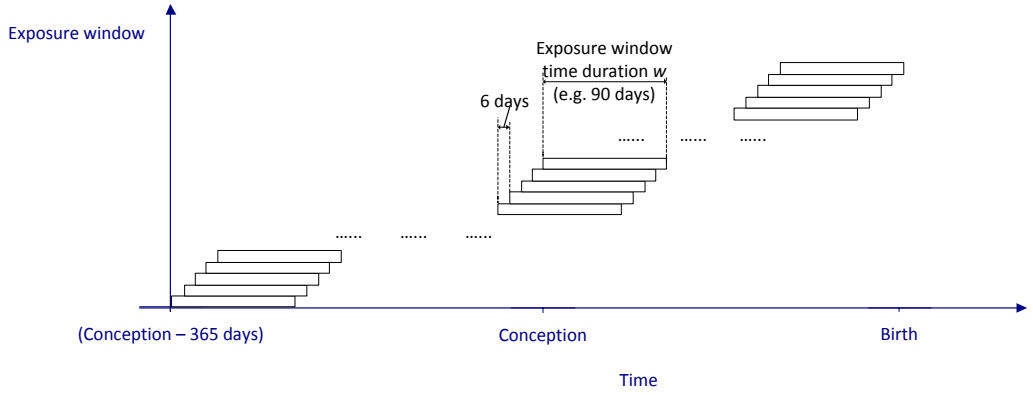

Figure 5.3 Illustration exposure window series (exposure window time duration (w) = 90 days, interval = 6 days)

A direct surrogate model was used to assess exposure to the TCEQ chemicals for the selected LBW cases and controls introduced in last section (Section 5.2.2). For a given chemical and an given exposure window, the estimated exposure intensity of an individual was the average ambient concentration values of the given chemical from the

closest monitoring site within that exposure window. However, if more than one fourth of the ambient concentration values within that exposure window were missing, the individual would be excluded from further analysis of that exposure window.

5.2.4. Identification of Potential Risk Factors and Critical Exposure Windows

For a given chemical and exposure window, exposure intensities were categorized into two groups (low exposure group: exposure intensities less than median, and high exposure group: greater than or equal to median) based on the control-mothers distribution of values. This study calculated the odds ratio (OR) of LBW between the high exposure group and the low exposure group. The low exposure groups were considered as reference groups for all analyses.

This study plotted the ORs against the exposure window series to generate a chart for each chemical. Based on these charts, the study identified ten TCEQ chemicals that were most likely to be associated with LBW in offspring using two criteria: (1) the highest statistically significant OR of the chemical was among the top ten in all chemicals; (2) the contingency table for calculating the odds ratio had all cell frequencies greater than or equal to 20. The second criterion was important, because odds ratio could be biased and show high variance due to small cell frequencies. These chemicals and their corresponding critical exposure windows were then used in further epidemiological analysis.

5.2.5. Epidemiological Analysis

For each critical exposure window (90-day windows) of the identified chemical, this study used binary logistic regression to validate the associations (OR and 95% confidence interval (CI)). The ORs were adjusted for some potential confounding variables that may be associated with the LBW. The potential confounding variables were selected based on the LBW related literature (e.g. child's sex, gestational weeks, maternal age, education, and race/ethnicity). Then this study applied a linear regression model with birth weight as a continuous dependent variable and all potential confounding variables (excluding air pollution variables) as independent variables to explore whether expected associations were observed (e.g., maternal age associated with lower birth weight). Only variables exhibiting statistically significant associations with birth weight were incorporated into the binary logistic regression model to calculate the adjusted odds ratios (aORs) representing TCEQ Chemical-LBW associations.

After examining the associations in the 90-day windows, this study changed the exposure window time duration (w) (e.g. 30-day windows, 60-day windows) and repeated the analysis of steps 3 to 5 (Sections 5.2.3 to 5.2.5) to examine associations at multiple temporal scales.

5.3. Results

5.3.1. Demographic Characteristics

The study population was the same as that described in Chapter 4, including a total of 94,106 LBW cases and 376,424 controls that were frequency matched to cases by year of birth. The descriptive statistics for the study population can be found in Table 4.2.

To protect the privacy of human subjects, the locations of the LBW cases and controls were not shown in the result.

5.3.2. Identified Potential Risk Factors and Critical Exposure Windows

For screening purpose, the surrounding area radius (*d*) was set to 1 km and the exposure window time duration (*w*) was set to 90 days. This study calculated the odds ratios (ORs) for each chemical in the 90-day exposure window series and plotted 367 odds ratio-exposure window charts for these 367 TCEQ chemicals. Based on these charts, ten chemicals were selected using the two criteria described in 5.2.4. The ten selected chemicals were (1) benzaldehyde, (2) 4-methyl-1-pentene, (3) hexanaldehyde,(4) sum of Photochemical Assessment Monitoring Stations (PAMS) target compound, (5) m-tolualdehyde, (6) n-undecane, (7) p-tolualdehyde, (8) ethylene dibromide, (9) n-butane, and (10) trans-crotonaldehyde. The odds ratio-exposure window charts of the ten TCEQ chemicals are shown in Figure 5.4.

The charts in Figure 5.4 show the trends of ORs in the exposure window series for the ten selected chemicals. The x coordinate represents the start date of exposure window ranging from one year before conception to the day of birth; the y coordinate shows the OR. Each small dot represents an OR which is not statistically significant; each big dot means that the OR is statistically significant; each diamond means that the OR is statistically significant and all cell frequencies of the corresponding contingency table are greater than or equal to 20. This study focused on the ORs represented by diamonds to identify critical exposure windows for the ten chemicals. As shown in Figure 5.4, most chemicals have more than one diamond in the OR-exposure window charts which indicated multiple critical exposure windows. However, some of the diamonds are

clustered and their corresponding exposure windows have significant overlaps. Therefore, this study only chose one representative diamond (exposure window) in each cluster for further analysis. The critical exposure windows of the ten chemicals are listed in Table 5.1.

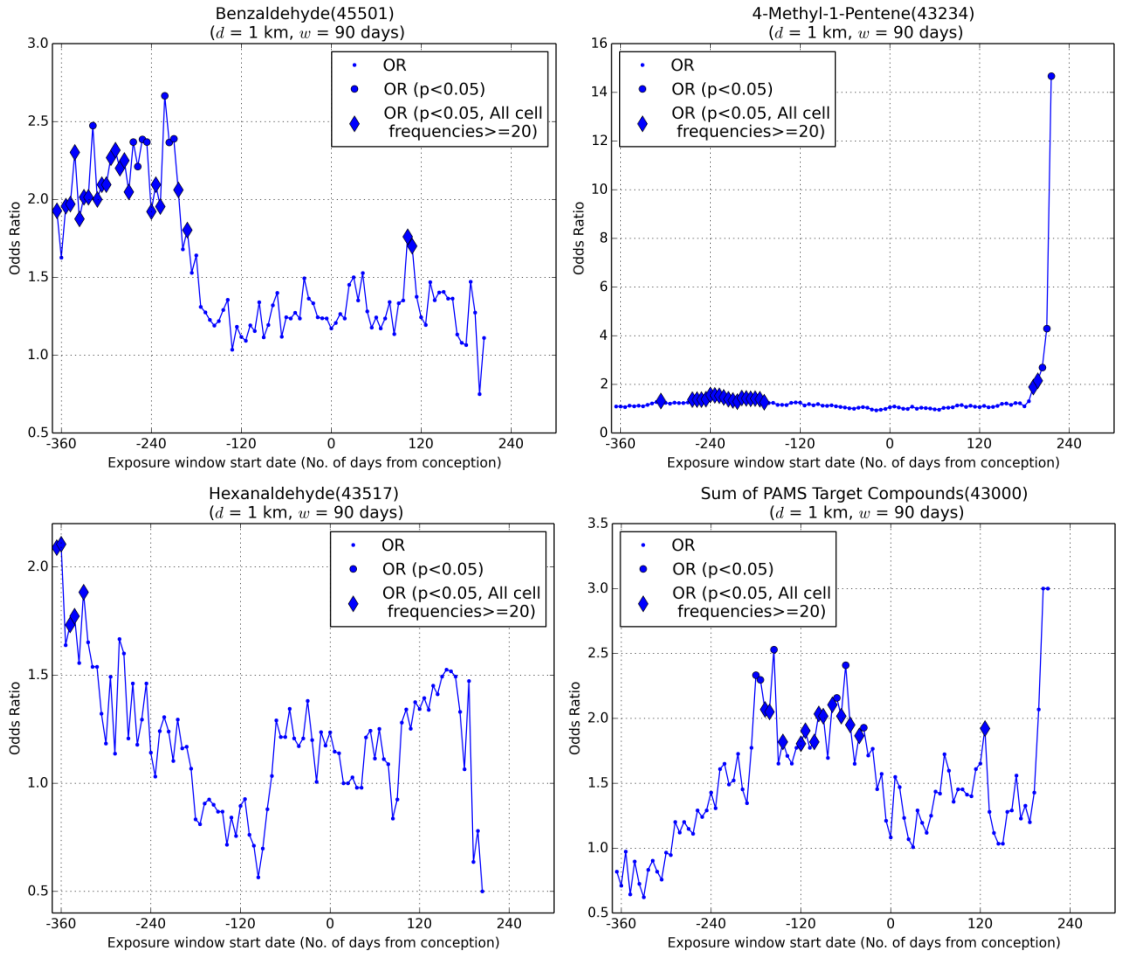

Figure 5.4 Odds ratio-exposure window charts for ten selected TCEQ chemicals.
(Note: *d* is the radius of area surrounding air quality monitors, *w* is the time duration of exposure windows)

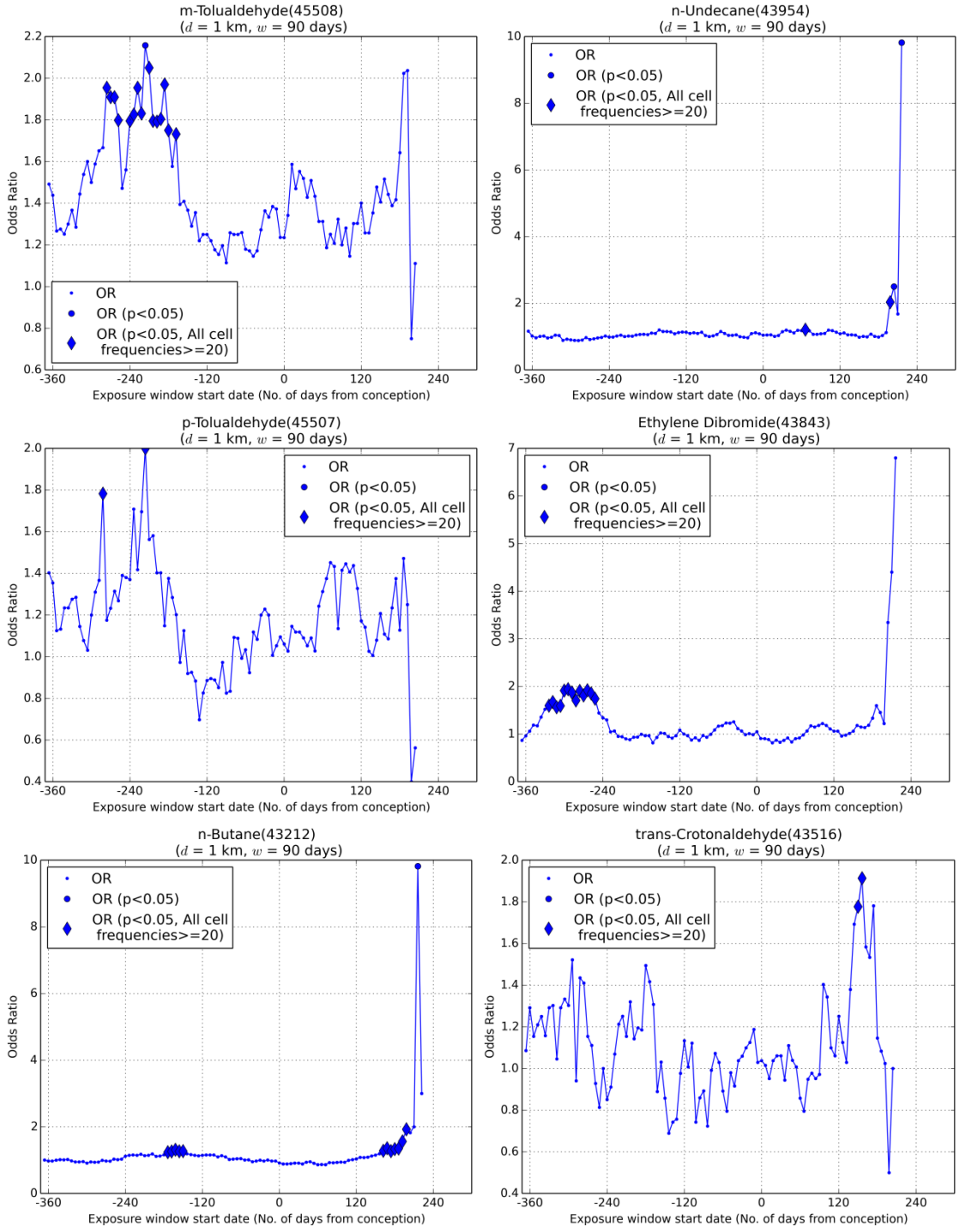

Figure 5.4-Continued

Table 5.1 Critical exposure windows (90-day windows) for selected TCEQ chemicals

Pollutant (TCEQ Chem Code)	Exposure Window[a]	Exposure Intensity[b]	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)
Benzaldehyde	-288 ~ -198	<=0.04	20	142	1.00 (Referent)	1.00 (Referent)
(45501)		>0.04	46	141	2.32 (1.30, 4.11)	2.66 (1.38, 5.12)
	102 ~ 192	<=0.04	28	162	1.00 (Referent)	1.00 (Referent)
		>0.04	49	161	1.76 (1.05, 2.94)	1.92 (1.09, 3.39)
4-methyl-1-pentene	-240 ~ -150	<=0.00	433	1583	1.00 (Referent)	1.00 (Referent)
(43234)		>0.00	127	297	1.56 (1.24, 1.97)	1.50 (1.18, 1.90)
	198 ~ 288	<=0.00	57	346	1.00 (Referent)	1.00 (Referent)
		>0.00	22	62	2.15 (1.23, 3.78)	2.04 (1.14, 3.65)
Hexanaldehyde	-360 ~ -270	<=0.04	22	143	1.00 (Referent)	1.00 (Referent)
(43517)		>0.04	46	142	2.11 (1.20, 3.68)	2.25 (1.24, 4.07)
Sum of PAMS	-168 ~ -78	<=140.39	20	115	1.00 (Referent)	1.00 (Referent)
target compounds		>140.39	41	114	2.07 (1.14, 3.75)	2.05 (1.10, 3.80)
(43000)	-78 ~ 12	<=140.16	20	116	1.00 (Referent)	1.00 (Referent)
		>140.16	41	113	2.10 (1.16, 3.81)	2.14 (1.14, 4.00)
	126 ~ 216	<=130.69	21	116	1.00 (Referent)	1.00 (Referent)
		>130.69	40	115	1.92 (1.07, 3.46)	2.13 (1.15, 3.94)
m-Tolualdehyde	-276 ~ -186	<=0.01	22	143	1.00 (Referent)	1.00 (Referent)
(45508)		>0.01	43	143	1.95 (1.11, 3.43)	2.00 (1.05, 3.81)
	-210 ~ -120	<=0.01	20	147	1.00 (Referent)	1.00 (Referent)
		>0.01	41	147	2.05 (1.15, 3.67)	1.91 (0.99, 3.69)
n-Undecane	66 ~ 156	<=0.01	285	1082	1.00 (Referent)	1.00 (Referent)
(43954)		>0.01	323	1016	1.21 (1.01, 1.45)	1.19 (0.99, 1.43)
	198 ~ 288	<=0.01	27	211	1.00 (Referent)	1.00 (Referent)
		>0.01	51	196	2.03 (1.23, 3.37)	2.00 (1.19, 3.35)
p-Tolualdehyde	-282 ~ -192	<=0.01	23	142	1.00 (Referent)	1.00 (Referent)
(45507)		>0.01	41	142	1.78 (1.02, 3.12)	1.79 (0.95, 3.36)
	-216 ~ -126	<=0.01	20	145	1.00 (Referent)	1.00 (Referent)
		>0.01	40	145	2.00 (1.12, 3.59)	1.84 (0.95, 3.57)
Ethylene dibromide	-294 ~ -204	<=0.00	373	1305	1.00 (Referent)	1.00 (Referent)
(43843)		>0.00	30	54	1.94 (1.23, 3.08)	1.97 (1.23, 3.14)

Table 5.1-Continued

Pollutant (TCEQ Chem Code)	Exposure Window[a]	Exposure Intensity[b]	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)
n-Butane	-162 ~ -72	<=0.39	246	965	1.00 (Referent)	1.00 (Referent)
(43212)		>0.39	322	964	1.31 (1.09, 1.58)	1.26 (1.04, 1.53)
	198 ~ 288	<=0.33	27	204	1.00 (Referent)	1.00 (Referent)
		>0.33	52	204	1.93 (1.16, 3.19)	1.79 (1.06, 3.02)
trans-Crotonaldehyde	156 ~ 246	<=0.04	23	135	1.00 (Referent)	1.00 (Referent)
(43516)		>0.04	44	135	1.91 (1.10, 3.34)	2.12 (1.16, 3.86)

[a] Days from date of conception
[b] Exposure intensity based on ambient concentrations from the closest monitoring site within that exposure window.
[c] Adjusted for child's sex, maternal race/ethnicity, age, education, and gestational length.

A total of eighteen critical exposure windows were related to the ten TCEQ chemicals (Table 5.1). Three chemicals (hexanaldehyde, ethylene dibromide, and trans-crotonaldehyde) had only one critical exposure window, six chemicals (benzaldehyde, 4-methyl-1-pentene, m-tolualdehyde, n-undecane, p-tolualdehyde, and n-butane) had two critical exposure windows, and one chemical (sum of PAMS target compounds) had three critical exposure windows. The temporal distribution of these critical exposure windows also showed certain patterns. Eleven critical exposure windows were identified before conception; six were after conception; and one covered both the time periods before and after conception. Most of the 90-day exposure windows before conception started from five or more months prior to conception, while the critical exposure windows after conception were found mainly in the second or third trimester.

Table 5.1 also provides ORs of LBW in offspring by exposure groups (low exposure group, high exposure group) in these eighteen 90-day exposure windows after adjusting for the confounding variables. Because the study population in the present study was identical with the one described in Chapter 4, the same confounding variables

were identified for this study based on the results in Table 4.4, including child's sex, gestational length, maternal age, education, and race/ethnicity. In Table 5.1, fourteen exposure windows showed statistically significant adjusted odds ratios (aORs), which meant that the risk of LBW in high exposure group was elevated when compared with low exposure group, and this high risk was statistically significant. The increased risk ranged from 26% to 166% (aOR: 1.26-2.66). The largest aOR was in the exposure window -288 to -198 (288 days before conception to 198 days before conception) of chemical benzaldehyde (aOR 2.66, 95% CI 1.38, 5.12). Eight critical exposure windows of six chemicals had aORs greater than 2.0, including benzaldehyde (aOR in window -288 ~ -198: 2.66, 95% CI 1.38, 5.12), 4-methyl-1-pentene (aOR in window 198 ~ 288: 2.04, 95% CI 1.14, 3.65), hexanaldehyde (aOR in window -360 ~ -270: 2.25, 95% CI 1.24, 4.07), sum of PAMS target compound (aOR in window -168 ~ -78: 2.05, 95% CI 1.10, 3.80; aOR in window -78 ~ 12: 2.14, 95% CI 1.14, 4.00; aOR in window 126 ~ 216: 2.13, 95% CI 1.15, 3.94), m-tolualdehyde (aOR in window -276 ~ -186: 2.00, 95% CI 1.05, 3.81), and trans-crotonaldehyde (aOR in window 156 ~ 246: 2.12, 95% CI 1.16, 3.86). For these six chemicals in these eight exposure windows, the mothers in high exposure groups had at least twice the risk of delivering a LBW baby when compared with the mothers in low exposure groups.

5.3.3. The TCEQ Chemical-LBW Associations at Multiple Temporal Scales

In order to investigate the details of the identified TCEQ Chemical-LBW associations at multiple temporal scales, a smaller exposure window time duration (30 days) was used as an example for the analysis. This study examined all of the 30-day exposure windows that were located within the eighteen selected 90-day critical exposure

windows (Table 5.1). Then, the 30-day critical exposure windows were selected based on the following criteria: (1) the exposure windows were related to statistically significant aORs; (2) the 30-day exposure windows had minimal overlaps with each other; and (3) all cell frequencies of the corresponding contingency table were greater than or equal to 20. Table 5.2 shows both 90-day critical exposure windows and 30-day critical exposure windows for the ten TCEQ chemicals identified previously. A total of eighteen representative 30-day critical exposure windows were extracted based on the criteria discussed above.

As shown in Table 5.2, at least one 30-day critical exposure window was found for twelve 90-day exposure windows. The aORs for these 30-day windows ranged from 1.22 to 2.55 with the highest aOR found for the window -270 to -240 (270 days before conception to 240 days before conception) of chemical benzaldehyde (aOR 2.55, 95% CI 1.32, 4.91). Table 5.2 also showed that no 30-day exposure window was identified for six of the 90-day windows. However, one should not conclude that there was no TCEQ Chemical-LBW association in any of these 30-day windows. It was likely that too few cases/controls were present in these 30-day windows and associations were biased and thus excluded.

Through comparing odds ratios in the 30-day windows and their corresponding 90-day windows, this study found several patterns. First, four 30-day exposure windows showed higher aORs than their corresponding 90-day windows, including 4-methyl-1-pentene (aOR of 1.96 in 30-day window -192 ~ -162 versus aOR of 1.50 in 90-day window -240 ~ -150), sum of PAMS target compound (aOR of 2.17 in 30-day window -102 ~ -72 versus aOR of 2.05 in 90-day window -168 ~ -78; aOR of 2.46 in 30-day

Table 5.2 Critical exposure windows at multiple temporal scales (90-day and 30-day windows) for selected TCEQ chemicals

Pollutant (TCEQ Chem Code)	Exposure Window[a] (time duration in days)	Exposure Intensity[b]	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)
Benzaldehyde (45501)	-288 ~ -198 (90)	<=0.04	20	142	1.00 (Referent)	1.00 (Referent)
		>0.04	46	141	2.32 (1.30, 4.11)	2.66 (1.38, 5.12)
	-270 ~ -240 (30)	<=0.04	21	141	1.00 (Referent)	1.00 (Referent)
		>0.04	44	141	2.10 (1.19, 3.70)	2.55 (1.32, 4.91)
	102 ~ 192 (90)	<=0.04	28	162	1.00 (Referent)	1.00 (Referent)
		>0.04	49	161	1.76 (1.05, 2.94)	1.92 (1.09, 3.39)
4-methyl-1-pentene (43234)	-240 ~ -150 (90)	<=0.00	433	1583	1.00 (Referent)	1.00 (Referent)
		>0.00	127	297	1.56 (1.24, 1.97)	1.50 (1.18, 1.90)
	-234 ~ -204 (30)	<=0.00	499	1777	1.00 (Referent)	1.00 (Referent)
		>0.00	64	152	1.50 (1.10, 2.04)	1.39 (1.01, 1.90)
	-192 ~ -162 (30)	<=0.00	500	1830	1.00 (Referent)	1.00 (Referent)
		>0.00	66	120	2.01 (1.47, 2.76)	1.96 (1.42, 2.70)
	198 ~ 288 (90)	<=0.00	57	346	1.00 (Referent)	1.00 (Referent)
		>0.00	22	62	2.15 (1.23, 3.78)	2.04 (1.14, 3.65)
	234 ~ 264 (30)	<=0.00	246	1332	1.00 (Referent)	1.00 (Referent)
		>0.00	31	103	1.63 (1.07, 2.49)	1.56 (1.01, 2.39)
Hexanaldehyde (43517)	-360 ~ -270 (90)	<=0.04	22	143	1.00 (Referent)	1.00 (Referent)
		>0.04	46	142	2.11 (1.20, 3.68)	2.25 (1.24, 4.07)
Sum of PAMS target compounds (43000)	-168 ~ -78 (90)	<=140.39	20	115	1.00 (Referent)	1.00 (Referent)
		>140.39	41	114	2.07 (1.14, 3.75)	2.05 (1.10, 3.80)
	-144 ~ -114 (30)	<=130.15	22	124	1.00 (Referent)	1.00 (Referent)
		>130.15	43	121	2.00 (1.13, 3.55)	1.90 (1.04, 3.48)
	-102 ~ -72 (30)	<=140.42	20	120	1.00 (Referent)	1.00 (Referent)
		>140.42	44	120	2.20 (1.22, 3.95)	2.17 (1.17, 4.04)
	-78 ~ 12 (90)	<=140.16	20	116	1.00 (Referent)	1.00 (Referent)
		>140.16	41	113	2.10 (1.16, 3.81)	2.14 (1.14, 4.00)
	-54 ~ -24 (30)	<=130.54	19	124	1.00 (Referent)	1.00 (Referent)
		>130.54	46	124	2.42 (1.34, 4.37)	2.46 (1.33, 4.55)
	-24 ~ 6 (30)	<=130.85	21	120	1.00 (Referent)	1.00 (Referent)
		>130.85	42	119	2.02 (1.13, 3.61)	2.03 (1.11, 3.71)
	126 ~ 216 (90)	<=130.69	21	116	1.00 (Referent)	1.00 (Referent)
		>130.69	40	115	1.92 (1.07, 3.46)	2.13 (1.15, 3.94)
	126 ~ 156 (30)	<=120.85	21	118	1.00 (Referent)	1.00 (Referent)
		>120.85	41	118	1.95 (1.09, 3.50)	2.00 (1.09, 3.67)
m-Tolualdehyde (45508)	-276 ~ -186 (90)	<=0.01	22	143	1.00 (Referent)	1.00 (Referent)
		>0.01	43	143	1.95 (1.11, 3.43)	2.00 (1.05, 3.81)

Table 5.2-Continued

m-Tolualdehyde (45508)	-270 ~ -240 (30)	<=0.01	22	141	1.00 (Referent)	1.00 (Referent)
		>0.01	43	141	1.95 (1.11, 3.44)	2.13 (1.13, 4.03)
	-210 ~ -120 (90)	<=0.01	20	147	1.00 (Referent)	1.00 (Referent)
		>0.01	41	147	2.05 (1.15, 3.67)	1.91 (0.99, 3.69)
	-180 ~ -150 (30)	<=0.01	22	145	1.00 (Referent)	1.00 (Referent)
		>0.01	44	145	2.00 (1.14, 3.51)	2.31 (1.22, 4.40)
n-Undecane (43954)	66 ~ 156 (90)	<=0.01	285	1082	1.00 (Referent)	1.00 (Referent)
		>0.01	323	1016	1.21 (1.01, 1.45)	1.19 (0.99, 1.43)
	198 ~ 288 (90)	<=0.01	27	211	1.00 (Referent)	1.00 (Referent)
		>0.01	51	196	2.03 (1.23, 3.37)	2.00 (1.19, 3.35)
p-Tolualdehyde (45507)	-282 ~ -192 (90)	<=0.01	23	142	1.00 (Referent)	1.00 (Referent)
		>0.01	41	142	1.78 (1.02, 3.12)	1.79 (0.95, 3.36)
	-216 ~ -126 (90)	<=0.01	20	145	1.00 (Referent)	1.00 (Referent)
		>0.01	40	145	2.00 (1.12, 3.59)	1.84 (0.95, 3.57)
	-192 ~ -162 (30)	<=0.01	22	144	1.00 (Referent)	1.00 (Referent)
		>0.01	41	144	1.86 (1.06, 3.29)	1.92 (1.02, 3.59)
	-162 ~ -132 (30)	<=0.01	25	148	1.00 (Referent)	1.00 (Referent)
		>0.01	47	148	1.88 (1.10, 3.21)	1.88 (1.04, 3.39)
Ethylene dibromide (43843)	-294 ~ -204 (90)	<=0.00	373	1305	1.00 (Referent)	1.00 (Referent)
		>0.00	30	54	1.94 (1.23, 3.08)	1.97 (1.23, 3.14)
n-Butane (43212)	-162 ~ -72 (90)	<=0.39	246	965	1.00 (Referent)	1.00 (Referent)
		>0.39	322	964	1.31 (1.09, 1.58)	1.26 (1.04, 1.53)
	-144 ~ -114 (30)	<=0.23	252	989	1.00 (Referent)	1.00 (Referent)
		>0.23	329	989	1.31 (1.08, 1.57)	1.26 (1.04, 1.52)
	-90 ~ -60 (30)	<=0.35	256	998	1.00 (Referent)	1.00 (Referent)
		>0.35	317	998	1.24 (1.03, 1.49)	1.22 (1.01, 1.47)
	198 ~ 288 (90)	<=0.33	27	204	1.00 (Referent)	1.00 (Referent)
		>0.33	52	204	1.93 (1.16, 3.19)	1.79 (1.06, 3.02)
	210 ~ 240 (30)	<=0.00	266	1054	1.00 (Referent)	1.00 (Referent)
		>0.00	355	1053	1.34 (1.12, 1.60)	1.29 (1.08, 1.56)
	228 ~ 258 (30)	<=0.05	171	904	1.00 (Referent)	1.00 (Referent)
		>0.05	232	903	1.36 (1.09, 1.69)	1.33 (1.07, 1.66)
trans-Crotonaldehyde (43516)	156 ~ 246 (90)	<=0.04	23	135	1.00 (Referent)	1.00 (Referent)
		>0.04	44	135	1.91 (1.10, 3.34)	2.12 (1.16, 3.86)
	198 ~ 228 (30)	<=0.04	25	149	1.00 (Referent)	1.00 (Referent)
		>0.04	44	146	1.80 (1.05, 3.09)	2.07 (1.16, 3.70)

[a]Days from date of conception
[b]Exposure intensity value based on ambient concentration values from the closest monitoring site within that exposure window.
[c]Adjusted for child's sex, maternal race/ethnicity, age, education, and gestational length.

window -54 ~ -24 versus aOR of 2.14 in 90-day window -78 ~ 12), and m-tolualdehyde (aOR of 2.13 in 30-day window -270 ~ -240 versus aOR of 2.00 in 90-day window -276 ~ -186). These patterns indicated that the TCEQ Chemical-LBW associations in these 30-day exposure windows were stronger than that in the corresponding 90-day windows.

Second, three 30-day exposure windows exhibited statistically significant aORs, while aORs in their corresponding 90-day exposure windows were not statistically significant. The three 30-day exposure windows included m-tolualdehyde (aOR in window -180 ~ -150: 2.31, 95% CI 1.22, 4.40), p-tolualdehyde (aOR in window -192 ~ -162: 1.92, 95% CI 1.02, 3.59; aOR in window -162 ~ -132: 1.88, 95% CI 1.04, 3.39). In this case, the strongest TCEQ Chemical-LBW associations actually existed in these 30-days exposure windows. However, when more time periods with weak associations were added to the 30-day windows to form a 90-day windows, the strength of the TCEQ Chemical-LBW associations were diluted.

Third, the rest of the 30-day exposure windows had lower aORs than their corresponding 90-day windows, which indicated that stronger associations existed in the 90-day windows. In this case, these finer temporal scales (30-day windows) should not be used for further analysis and decision-making.

5.4. Discussions and Conclusions

This large population-based study combined a spatio-temporal method with a case-control design to investigate the association between maternal exposure to TCEQ chemicals and LBW in offspring at multiple temporal scales. This study selected ten chemicals (benzaldehyde, 4-methyl-1-pentene, hexanaldehyde, sum of PAMS target

compound, m-tolualdehyde, n-undecane, p-tolualdehyde, ethylene dibromide, n-butane, and trans-crotonaldehyde) from all of the 367 TCEQ chemicals and identified critical maternal exposure windows that showed the strongest associations with LBW in offspring. The study found that case-mothers were more likely to be exposed to higher intensities of these ten chemicals within the critical exposure windows than control-mothers, based on their residence locations and the TCEQ air quality monitoring data. In this study, the identified critical exposure windows had flexible time durations (e.g. 30 days, 90 days) and starting times (e.g. before conception or after conception). Critical exposure windows before conception were discovered in eight of the ten TCEQ chemicals. Critical exposure windows after conception were identified in the second or third trimester of pregnancy in six of the ten chemicals.

Among the ten chemicals, except for the sum of Photochemical Assessment Monitoring Stations (PAMS) target compound, the inhalation of the other nine chemicals was reported to have adverse health effects, including eye, mucous membrane, and respiratory tract irritations (NOAA, 2015). Data collected at the PAMS sites were ozone, oxides of nitrogen (NO_x), and a target list of volatile organic compounds (VOC) (U.S. EPA 2015a). The sum of PAMS target compounds was an integrated measurement of the above chemicals. Results of the present study indicated that higher exposure to the combination of these chemicals in mothers were related to higher LBW risks in offspring. The associations between maternal exposure to these ten chemicals and LBW in offspring have not been reported. These discoveries of TRI chemical-LBW associations in the present study created new opportunities for further epidemiological, biological, and toxicological studies.

Very few studies have focused on the associations between maternal exposure before conception and LBW in offspring. A study using animal test found that maternal exposure to urban ambient particulate matter before conception were negatively associated with birth weight (Veras 2009). Compared with the reference group, the exposed group had an average of 20% lower weight (Veras 2009). In a Finnish study population, the risk of low birth weight (<3000 g) was related to maternal exposure to combination of welding fumes (WF) and metal dusts or fumes (MD/F) during the three months before pregnancy (aOR 2.01, 95% CI 1.06, 3.80) (Quansah and Jaakkola 2009). The present study also found two critical exposure windows within the three months before pregnancy, including sum of PAMS target compound (aOR in window -54 ~ -24: 2.46, 95% CI 1.33, 4.55) and n-butane (aOR in window -90 ~ -60: 1.22, 95% CI 1.01, 1.47). However, most of the critical exposure windows (30-day and 90-day) before conception in the present study were found in earlier time periods. Fourteen exposure windows started from six or more months before conception, and six exposure windows started between three to six months before conception. The wide temporal coverage before conception of critical exposure window indicated that mothers who were prepared for pregnancy should pay close attention to the air quality in their living environment well before conception.

Most of the critical exposure windows after conception in the present study were located within the second and third trimesters of pregnancy. Several previous studies on air pollution-LBW associations also identified the second and third trimesters of pregnancy as critical exposure windows. In a Brazil study population, PM_{10} exposure in the third trimester of pregnancy was associated with the LBW in offspring (OR between

fourth quartile and first quartile of exposure: 1.26, 95% CI 1.14, 1.40) (Romao et al. 2013). In a study conducted in Massachusetts, USA for a 9-year period (2000-2008), the authors found that $PM_{2.5}$ exposure during the last 30 days of pregnancy contributed to LBW in offspring (Kloog et al. 2012). In a Pittsburgh, Pennsylvania, USA study, the PM_{10} exposure in the first and second trimesters was associated with elevated risk of LBW. The odds ratios of LBW per inter-quartile range increase in PM_{10} during these two trimesters were 1.13 (95% CI 1.02, 1.25) and 1.10 (95% CI 1.00, 1.22) respectively (Xu et al. 2011).

In another study conducted in Massachusetts and Connecticut, USA, Bell, Ebisu, and Belanger (2007) discovered air pollution-LBW associations in the third trimester for PM_{10}, the first and third trimesters for CO, the first trimester for NO_2 and SO_2, and the second and third trimesters for $PM_{2.5}$. In a Spanish study with INMA (Environment and Childhood) cohort, an estimated reduction of 102 g (95% CI 28g - 146g) in birth weight was associated with an interquartile range increase in BTEX (benzene, toluene, ethyl benzene, and xylene) exposure in the second trimester (Aguilera et al. 2009). Compared with previous studies, the critical exposure windows in the present study showed some flexibility and did not exactly follow the trimester's time window. Additionally, although most of the critical exposure windows were found in the second and third trimesters of pregnancy, it did not imply that TCEQ chemical exposure in other exposure windows would not increase the risk of LBW in offspring.

The combination effect of exposure windows before and after conception was also considered in previous LBW study (Quansah and Jaakkola 2009). However, the exposure window sizes were restricted to 3 months or trimester. In the present study, the

exposure windows were more flexible. Two exposure windows that covered both before and after conception were identified, including the window -78 ~ 12 (aOR 2.14, 95% CI 1.14, 4.00) and window -24 ~ 6 (aOR 2.03, 95% CI 1.11, 3.71) of the sum of PAMS target compound.

This study proposed an interactive method to investigate air pollution-LBW associations in different exposure windows. Users of this method could not only interactively select chemicals based on different criteria, but also investigate associations across multiple spatial and temporal scales by assigning different values to the model parameters. Although the study showed results for only ten chemicals and their critical exposure windows, one can always use the method proposed in the present study to investigate more exposure windows and chemicals, as long as the corresponding monitoring data exist. In order to improve the interaction experience, a software package can be developed in the future based on the model and procedures of the present study.

With different values of exposure window time duration (w), the model in the present study has the capacity to examine TCEQ Chemical-LBW associations across multiple temporal scales, e.g. 90 days and 30 days. When choosing an exposure window time duration (w), one needs to balance between temporal scale and sample size. If large exposure window time durations (w) were used, e.g. one-year exposure window, results would only reflect associations between long-term exposure and health effects; some critical exposure windows of smaller time durations would be ignored. However, if the time durations of exposure windows were too small, then small sample size of LBW cases and controls would be used to measure the association. In this situation, it is highly likely that the low cell frequencies in the contingency table would introduce bias in the

OR, and cause high variances. For example, a significant effect of exposure within the exposure window of one week or a few days on LBW risks might appear by chance due to this high variance. Therefore, the study recommended using 90 days as an initial exposure window time duration (*w*) for the screening process. If any interesting results (key chemicals and critical exposure windows) were discovered and the sample size permitted, one could then apply smaller exposure windows to further explore the data. However, if the smaller exposure windows showed weaker associations than the larger exposure windows, the larger windows should be retained as the critical exposure windows for further analysis. The exploration for association at a finer temporal scale could stop when the number of cases/controls is not sufficient for any meaningful analysis.

The surrounding area radius (*d*) might also affect the results, as mentioned in Section 2.2.3. However, if the surrounding area radius (*d*) were too large, the spatially homogeneous assumption would be violated. In contrast, if the surrounding area radius (*d*) were too small, there would be not enough LBW cases and controls available to quantify the association. In order to test the effect of surrounding area radius (*d*), this study repeated the analysis of steps 2 to 5 (Section 5.2.2 to5.2.5) using 2 km as the surrounding area radius (*d*). Figure 5.5 shows the odds ratio-exposure window charts for the ten identified chemicals. The patterns of associations were very similar to that from the analysis based on 1 km (Figure 5.4). However, when larger surrounding area radius (*d*) was used, larger bias and uncertainties would be introduced in the estimated exposure due to the air dispersion process. Therefore, the study recommended that, as long as the sample size is sufficiently large, one should use as small a radius as possible to minimize

bias. The big data used in the present study provided some advantages (e.g., enough sample size and study power) to investigate the LBW risks using small surrounding area radius (*d*).

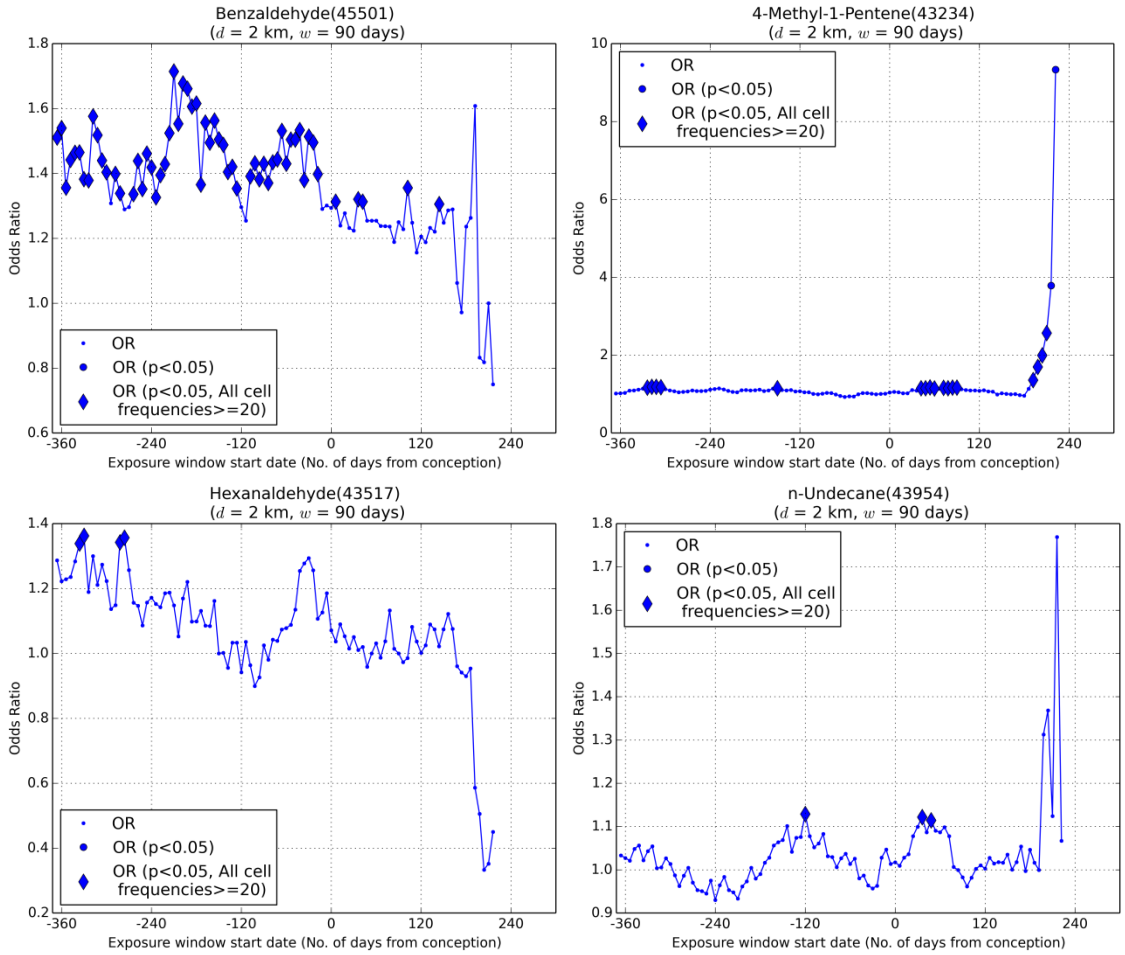

Figure 5.5 Odds ratio-exposure window charts for ten selected TCEQ chemicals (*d* = 2 km). (Note: *d* is the radius of area surrounding air quality monitors, *w* is the time duration of exposure windows)

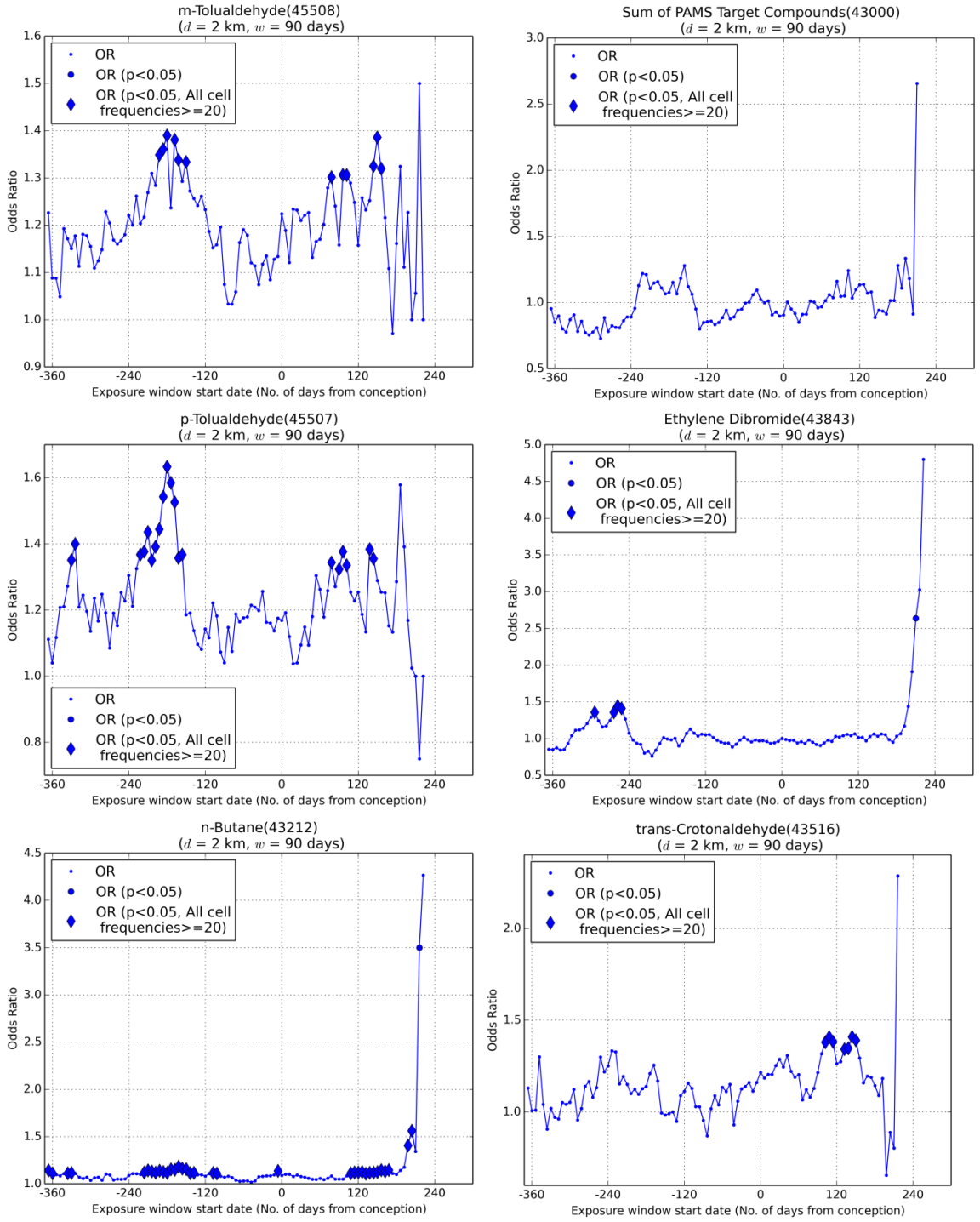

Figure 5.5-Countinued

Several limitations should be observed in the present study. The chemical exposure in different exposure windows could be correlated. For studies using trimesters

as exposure windows, the exposure in later trimesters could be adjusted for earlier trimesters to avoid covariance among variables representing trimester exposures (Bell, Ebisu, and Belanger 2007). However, when estimating exposure in a certain exposure window, the present study did not adjust for exposure in earlier windows. The reasons were as follows. First, the exposure window was flexible with various time durations and starting times. It would be difficult, if not impossible, to adjust for exposure in all earlier windows. Second, because the present study also considered exposure windows before conception, those exposure windows should also be included in the "earlier windows." However, it would be difficult to determine the earliest window before conception that need to be adjusted. Third, the monitoring data were not complete. Too many exposure windows would have missing exposure values if the study adjusted for all of the earlier windows. Nevertheless, if all missing values in the air quality monitoring data were deleted, the sample size would sharply shrink and the study power would be negatively affected.

This study did not account for the multiple testing problem, which was defined as "By chance, the probability of wrongly rejecting one or more null hypotheses increases in proportion to the number of comparisons tested" (Hsu 1996). Efird and Nielsen(2008) proposed a method to compute multiplicity corrected confidence intervals for odds ratios. However, it would be computational intensive to use this method, especially in the present study which calculated odds ratio for hundreds of times. The present study worked as a data mining tool to filter specific chemicals and exposure windows for further study, so it was still acceptable to have some false discoveries (type I errors), that can be verified in further epidemiological, biological, and toxicological studies. As an

alternative, this study could also lower the p-value when choosing the critical exposure windows to alleviate the multiple testing problem.

This study was also limited by the fact that the coverage of the air quality monitoring data were not complete at times. The study used an ambient monitor-based method for air pollution exposure assessment. Because only chemicals with adequate monitoring records could have accurate estimated exposure, the study excluded many chemicals whose monitoring records were incomplete during the screening process. Therefore, the study calls for a more thorough collection of monitoring data in the future, especially for chemicals that have been found to be associated with LBW in previous studies but have few air quality monitoring records. For chemicals with incomplete air quality monitoring data, one can only conclude that there was no evidence on their effect on LBW in the existing literature, but should not infer that no association existed at all. The spatial distribution of the monitoring sites might also affect the results. The study found that most of the sites were located in urban areas and concentrated in a few big cities, and therefore exposure intensities in suburban area were not well represented. One possible solution is to create evenly distributed sampling points by interpolating the existing monitoring values using the Kriging method. However, Whitworth et al. (2011) found that the Kriging method would introduce more uncertainties, which in turn affect the analysis results. Further studies are needed to understand and mitigate the effect of geographic distribution of sampling points.

This study assumed that maternal residential addresses did not change within the period of one year before conception to the day of delivery. While it was true for most mothers, some mothers may change their residences during pregnancy (Canfield et al.

2006; Lupo et al. 2010) and the movement may cause exposure misclassifications for those mothers. However, since the movement tended to be short distance movement in most cases, its effect in exposure assessment might be minimal (Lupo et al. 2010). Since the exposure assessment was based on the maternal residential address at delivery, the exposure windows closer to the time of delivery are less likely to have exposure misclassification from residential mobility during pregnancy. In other words, while this study investigated different exposure windows, the study have better ability to investigate some exposure windows (close to the time of delivery) than others. This can partial explain why the critical exposure windows after conception were found mainly in the second or third trimester in this study.

6. THE NUCLEAR FACILITIES-LBW ASSOCIATION STUDY

6.1. Introduction

With increasing requirements for power in human lives, more and more nuclear facilities were built for power generation. However, nuclear facility accidents (Three Mile Island (1979), Chernobyl (1986), and Fukushima Daiichi (2011), etc.) have warned people the danger of nuclear power and brought the nuclear facilities into view. In addition to the obviously disastrous effect after nuclear facilities accidents, the potential long-term adverse health effects caused by living in the proximity to the nuclear facilities have also become a public concern. Therefore, many studies have attempted to discover the relation between residential proximity to nuclear facilities and health outcomes. However, as noted in Section 2.3, no consistent conclusion has been reached. Moreover, low birth weight (LBW), the target health effect in this study, has been given little attention. Existing findings were not enough to make conclusions on the association between maternal residential proximity to nuclear facilities and LBW in offspring. Therefore, this study examined the association through spatial analysis and statistical analysis on massive georeferenced data.

The study discussed in this chapter intends to answer the research question 3 elaborated in Chapter 1. The remainder of this chapter is organized as follows. Section 6.2 provides a detailed description of the data and methodology. The results of Nuclear Facilities-LBW associations are presented in Section 6.3. Finally, Section 6.4 wraps up the chapter with a discussion of the results and a presentation of the conclusions.

6.2. Data and Methodology

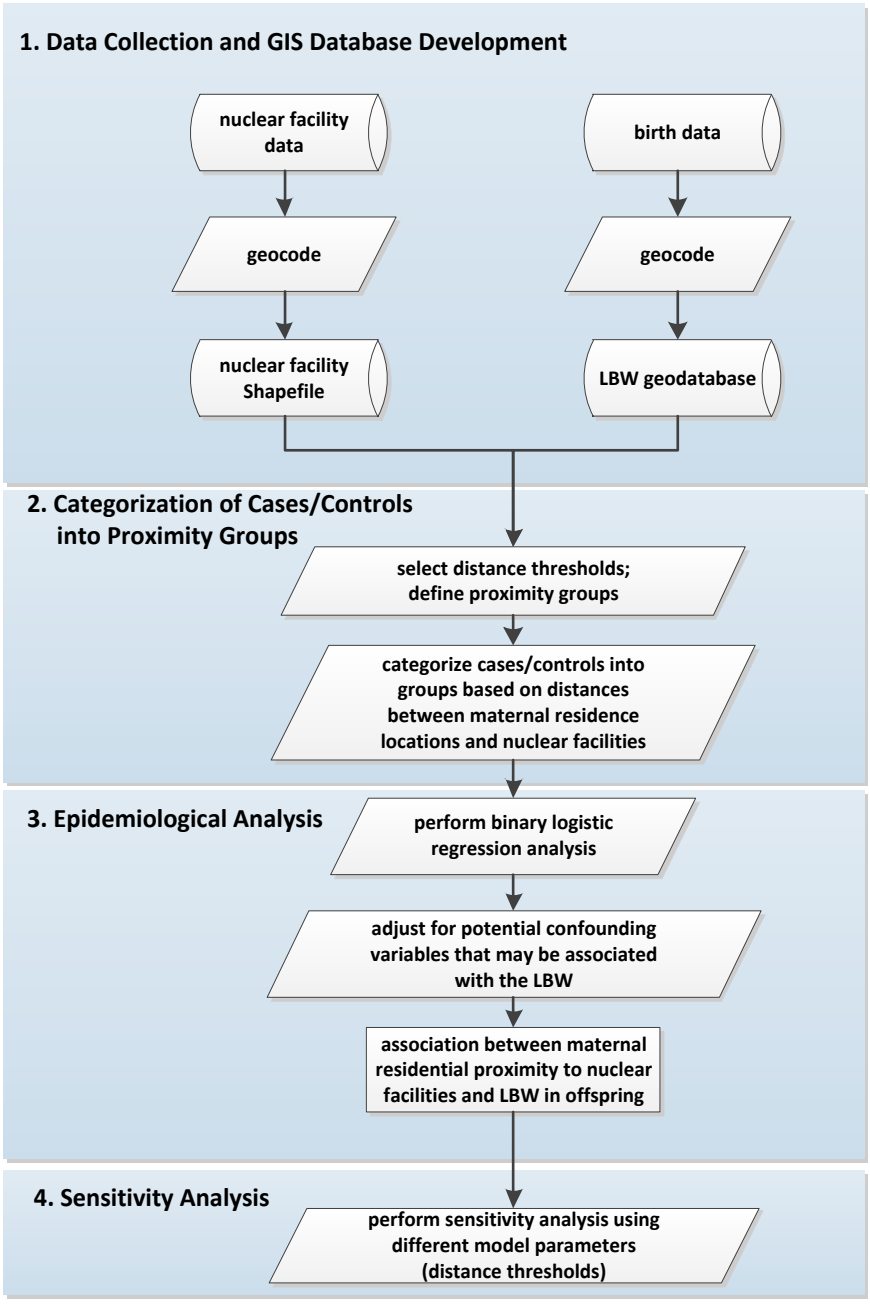

Figure 6.1 Framework of methodology: The Nuclear Facilities-LBW association study

This study used a case-control study design together with the proximity-based model (as noted in Section 2.3.3) to investigate the Nuclear Facilities-LBW association,

and then conducted sensitivity analysis on distance thresholds of the proximity-based model to further validate the results. The methodology framework consists of four steps as shown in Figure 6.1.

6.2.1. Data Collection and GIS Database Development

The analyses of this study involved nuclear facility data and birth data. The details of the two datasets are as follows.

6.2.1.1. Nuclear Facility Data

The Nuclear facility data were obtained from United States Nuclear Regulatory Commission (U.S. NRC) as described in Section 3.2.1.3. This study extracted the nuclear facilities in operation during 1996-2008 in Texas. There were two nuclear plants with four units selected (Table 3.1). The nuclear facilities were geocoded using ESRI ArcGIS 10.1. The output file was an ESRI shapefile containing both locations and corresponding non-spatial attributes of nuclear facilities.

6.2.1.2. Birth Data

Birth certificate data were obtained from the Center for Health Statistics in the Texas Department of State Health Services. This study selected LBW cases and controls from the birth certificates based on the criteria and procedure described in Section 3.2.2. Each birth certificate record included the following variables: geocoded coordinates of maternal residential address at delivery; birth location; birth weight; year of birth; plurality; child's sex; prenatal care; mother's characteristics (age at delivery, race/ethnicity, education, marital status, gestational age in weeks, date for last menstrual period; and tobacco use during pregnancy); and father's characteristics (age,

race/ethnicity, and education). Then, this study constructed a LBW geodatabase containing both the georeferenced locations of LBW cases and controls, as well as non-spatial variables obtained from the birth certificates.

6.2.2. Categorization of Cases/Controls into Proximity Groups

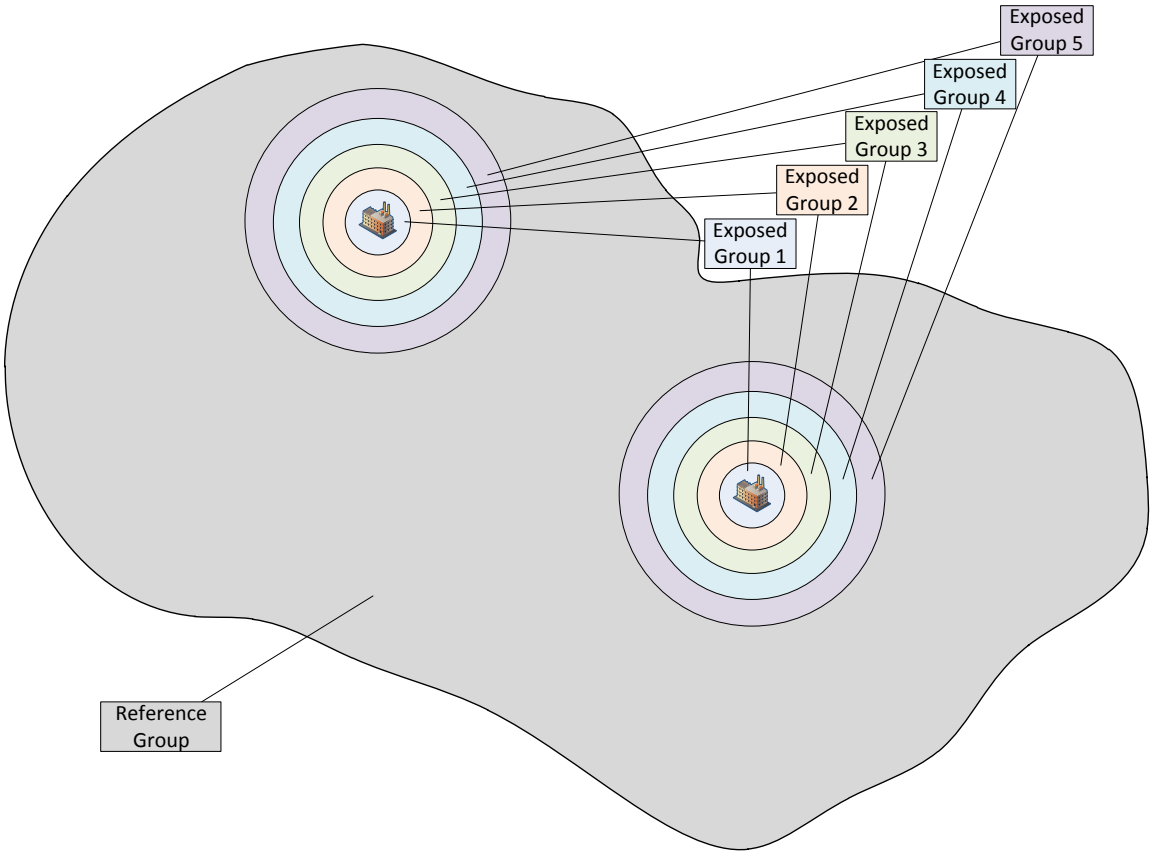

Figure 6.2 Different proximity groups to nuclear facilities

This study first selected distance thresholds, which defined multiple groups of proximity to nuclear facilities (Figure 6.2). Then the LBW cases and controls were categorized into these proximity groups based on distances between their maternal residence locations and nuclear facilities. In most studies on health effect near nuclear facilities, cases and controls that lived more than 50 km away from any nuclear facilities were categorized into the reference group as shown in Table 2.5. Accordingly, this study

also used 50 km as the distance threshold for the reference group. Distance within 50 km was further divided into five equal interval groups (0-10 km, 10-20 km, 20-30 km, 30-40 km, and 40-50 km) using threshold 10 km, 20 km, 30 km, and 40 km (Figure 6.2). These five proximity groups were considered as exposed groups in the following analysis.

6.2.3. Epidemiological Analysis

This study applied binary logistic regression to examine the association between maternal residential proximity to nuclear facilities and LBW case/control status. In the analyses of odds ratios (ORs) associated with different proximity groups, the study used the Wald statistic to test the significance of linear trends among ORs. The ORs were adjusted for several potential confounding variables that might be associate with the LBW.

These potential confounding variables were first chosen based on the LBW-related literature (e.g. child's sex, gestational weeks, maternal age, education, and race/ethnicity.). Then this study applied a linear regression model with birth weight as a continuous dependent variable and all potential confounding variables (excluding residential proximity variable) as independent variables to explore whether expected associations were observed (e.g., maternal age associated with lower birth weight). Variables exhibiting statistically significant associations with birth weight were incorporated into the binary logistic regression model to calculate the adjusted odds ratios (aORs) representing the Nuclear Facilities-LBW association.

6.2.4. Sensitivity Analysis

Sensitivity analyses on model parameters (distance thresholds) were conducted to validate the results. Based on the original analysis group, this study created three groups of sensitivity analysis by changing both the distance threshold of reference group and the distance intervals of exposed groups as shown in Table 6.1. For each sensitivity analysis group, the study used the same epidemiological analysis procedure (as Section 6.2.3) to examine the Nuclear Facilities-LBW association. Results were compared with the original analysis group to examine how model parameters may affect the results.

Table 6.1 Distance thresholds for original analysis and sensitivity analyses

Group ID	Reference Group	Exposed Groups	Description
Original Analysis	>50 km	0-10 km, 10-20 km, 20-30 km, 30-40 km, 40-50 km	Proximity groups of original analysis.
Sensitive Analysis I	>100 km	0-10 km, 10-20 km, 20-30 km, 30-40 km, 40-50 km	Increase the distance threshold of reference group.
Sensitive Analysis II	>50 km	0-5 km, 5-10 km, 10-15 km, 15-20 km, 20-25 km	Decrease the distance interval of exposed groups.
Sensitive Analysis III	>50 km	0-20 km, 20-40 km	Increase the distance interval of exposed groups.

6.3. Results

A total of 94,106 LBW cases and 3,386,971 controls in Texas during 1996-2008 were selected in this study for analysis. Table 6.2 shows a comparison between cases and controls by child's sex, mother's age at delivery, mother's race/ethnicity, gestational length, year of birth, public health region of maternal residence at the time of delivery, and mother's education. The LBW cases comprised 2.7% of the total births, 2.3% of the male births, and 3.2% of the female births. Compared with the control-mothers, case-

mothers were more likely to be non-Hispanic black, or have younger delivery age, shorter gestational length, or less education.

Table 6.2 Selected characteristics of low birth weight cases and controls, Texas, 1996-2008

Characteristic		Cases (n= 94,106)		Controls (n=3,386,971)		Total (n=3,481,077)	
		n	%	n	%	n	%
Child's sex	Male	39,787	42.3	1,728,516	51.0	1,768,303	50.8
	Female	54,319	57.7	1,658,455	49.0	1,712,774	49.2
Mother's age at delivery (years)	11-19	18,791	20.0	465,020	13.7	483,811	13.9
	20-24	28,850	30.7	938,984	27.7	967,834	27.8
	25-29	22,139	23.5	928,873	27.4	951,012	27.3
	30-34	14,898	15.8	692,733	20.5	707,631	20.3
	35-39	7,470	7.9	303,232	9.0	310,702	8.9
	>40	1,957	2.1	58,079	1.7	60,036	1.7
	Unknown	1	<0.1	50	<0.1	51	<0.1
Mother's race/ethnicity	Non-Hispanic White	27,642	29.4	1,287,870	38.0	1,315,512	37.8
	Non-Hispanic black	18,344	19.5	359,367	10.6	377,711	10.9
	Hispanic	43,366	46.1	1,602,992	47.3	1,646,358	47.3
	Others, non-Hispanic	4,754	5.1	136,742	4.0	141,496	4.1
Gestational length (weeks)	37	29,089	30.9	350,204	10.3	379,293	10.9
	38	25,426	27.0	748,946	22.1	774,372	22.2
	39	18,488	19.6	969,056	28.6	987,544	28.4
	40	10,578	11.2	730,301	21.6	740,879	21.3
	41	5,307	5.6	351,559	10.4	356,866	10.3
	42	2,830	3.0	132,644	3.9	135,474	3.9
	43	1,634	1.7	71,204	2.1	72,838	2.1
	44	754	0.8	33,057	1.0	33,811	1.0
Year of birth	1996	5,739	6.1	221,212	6.5	226,951	6.5
	1997	5,750	6.1	224,665	6.6	230,415	6.6
	1998	5,910	6.3	228,012	6.7	233,922	6.7
	1999	5,974	6.3	234,588	6.9	240,562	6.9
	2000	6,333	6.7	241,921	7.1	248,254	7.1
	2001	6,433	6.8	244,912	7.2	251,345	7.2
	2002	7,023	7.5	259,662	7.7	266,685	7.7
	2003	7,166	7.6	259,517	7.7	266,683	7.7
	2004	7,535	8.0	266,609	7.9	274,144	7.9
	2005	8,451	9.0	286,653	8.5	295,104	8.5
	2006	9,071	9.6	301,555	8.9	310,626	8.9
	2007	9,236	9.8	309,295	9.1	318,531	9.2
	2008	9,485	10.1	308,370	9.1	317,855	9.1

Table 6.2-Countinued

Characteristic		Cases (n= 94,106)		Controls (n=3,386,971)		Total (n=3,481,077)	
		n	%	n	%	n	%
Public health region	1	3,855	4.1	109,923	3.2	113,778	3.3
	2	1,992	2.1	68,861	2.0	70,853	2.0
	3	24,253	25.8	960,736	28.4	984,989	28.3
	4	3,230	3.4	104,574	3.1	107,804	3.1
	5	2,561	2.7	75,028	2.2	77,589	2.2
	6	23,094	24.5	847,952	25.0	871,046	25.0
	7	9,236	9.8	365,936	10.8	375,172	10.8
	8	10,324	11.0	339,109	10.0	349,433	10.0
	9	2,565	2.7	74,400	2.2	76,965	2.2
	10	4,183	4.4	134,086	4.0	138,269	4.0
	11	8,813	9.4	306,366	9.0	315,179	9.1
Education	< High School	33,963	36.1	1,021,964	30.2	1,055,927	30.3
	High School	30,200	32.1	978,790	28.9	1,008,990	29.0
	> High School	29,082	30.9	1,359,124	40.1	1,388,206	39.9
	Unknown	861	0.9	27,093	0.8	27,954	0.8

Table 6.3 shows results for the linear regression model using birth weight as a continuous dependent variable and all potential confounding variables as independent variables. All variables in Table 6.3 demonstrated statistically significant associations with birth weights. Specifically, female infants tended to have lower birth weights; mothers with less education or younger age had lower birth weights in offspring; the shorter gestational lengths were also associated with lower birth weights. Moreover, when compared to Non-Hispanic White mothers, mothers from other races/ethnicity groups were more likely to have infants with lower birth weights. Therefore, the ORs for the association between maternal residential proximity and LBW need to be adjusted for child's sex, maternal race/ethnicity, age, education, and gestational length. Because of the uneven distribution of births in both time and space (Table 6.2), the ORs were also adjusted for the year of birth and public health region of maternal residence.

Table 6.3 Difference in birth weight associated with selected non-proximity variables (95% confidence interval)

Variable	Difference in birth weight (g)	
Child's Sex		
Male (reference)		
Female	-123.7	(-124.7, -122.8)
Mother's race/ethnicity		
Non-Hispanic White (reference)		
Non-Hispanic Black	-160.6	(-162.2, -159.0)
Hispanic	-41.7	(-42.8, -40.6)
Others, non-Hispanic	-183.2	(-185.6, -180.7)
Mother's education		
High School (reference)		
< High School	-7.7	(-9.0, -6.5)
> High School	22.1	(20.9, 23.3)
Mother's age (years)		
30-34 (reference)		
11-19	-157.4	(-159.1, -155.6)
20-24	-96.0	(-97.4, -94.6)
25-29	-35.4	(-36.8, -34.1)
35-39	12.5	(10.6, 14.3)
>39	-1.7	(-5.4, 2.0)
Gestational length (weeks)		
40 (reference)		
37	-325.4	(-327.1, -323.7)
38	-184.9	(-186.3, -183.5)
39	-79.9	(-81.2, -78.6)
41	36.4	(34.6, 38.2)
42	-8.1	(-10.7, -5.6)
43	-32.0	(-35.4, -28.7)
44	-15.0	(-19.9, -10.2)

Table 6.4 displays the association between proximity groups and LBW in the original analysis group. The aORs were 0.91 (confidence interval (CI) 0.81, 1.03) for group 40-50 km; 0.98 (CI 0.84, 1.13) for group 30-40 km; 0.95 (CI 0.79, 1.15) for group 20-30 km; 0.86 (CI 0.70, 1.04) for group 10-20 km; and 0.98 (CI 0.59, 1.61) for group 0-10 km when comparing with the reference group (>50 km). The aORs for the five exposed groups were not statistically significant, which meant that LBW risks in the

exposed groups were not significantly different from that in the reference group. In proximity groups 40-50 km, 30-40 km, and 10-20 km, the unadjusted ORs were statistically significant and smaller than one. However, after adjusting for the confounding variables, none of the three proximity groups showed statistically significant aORs. Therefore, the statistically significant unadjusted ORs were actually caused by the confounding variables rather than the maternal residential proximity to nuclear facilities. Moreover, there was no statistically significant linear trend for these aORs ($p = 0.066$). The results of the original analysis indicated that maternal residential proximity to nuclear facilities was not associated with LBW in offspring.

Table 6.4 Maternal residential proximity to nuclear facilities and LBW in offspring (Original analysis)

Proximity (km)	Cases		Control		Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	p-value for trend
	n	%	n	%			
>50	92,526	99.23	3,327,655	99.04	1.00 (Referent)	1.00 (Referent)	0.066
40-50	297	0.32	14,112	0.42	0.76 (0.68, 0.85)	0.91 (0.81, 1.03)	
30-40	188	0.20	7,946	0.24	0.85 (0.74, 0.98)	0.98 (0.84, 1.13)	
20-30	111	0.12	4,351	0.13	0.92 (0.76, 1.11)	0.95 (0.79, 1.15)	
10-20	106	0.11	5,047	0.15	0.76 (0.62, 0.92)	0.86 (0.70, 1.04)	
0-10	16	0.02	721	0.02	0.80 (0.49, 1.31)	0.98 (0.59, 1.61)	

[a]Adjusted for birth year, public health region, child's sex, maternal race/ethnicity, age, education, and gestational length.

Table 6.5 shows results of sensitivity analysis on model parameters (distance thresholds). The patterns of results were very similar to the original analysis. Although some unadjusted ORs were statistically significant, none of the aORs was statistically significant. The trends were not monotonic in any of the three sensitivity analysis groups. Consequently, the sensitivity analysis indicated that the model parameters did not

substantially affect the result. The Nuclear Facilities-LBW association did not change significantly when different distance thresholds were used.

Table 6.5 Maternal residential proximity to nuclear facilities and LBW in offspring (Sensitivity Analyses).
(a) Sensitivity analysis I; (b) Sensitivity analysis II; (c) Sensitivity analysis III
(a)

Proximity (km)	Cases		Control		Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	p-value for trend
	n	%	n	%			
>100	79,570	99.11	2,838,585	98.88	1.00 (Referent)	1.00 (Referent)	0.077
40-50	297	0.37	14,112	0.49	0.75 (0.67, 0.84)	0.92 (0.82, 1.03)	
30-40	188	0.23	7,946	0.28	0.84 (0.73, 0.98)	0.98 (0.85, 1.14)	
20-30	111	0.14	4,351	0.15	0.91 (0.75, 1.10)	0.95 (0.79, 1.15)	
10-20	106	0.13	5,047	0.18	0.75 (0.62, 0.91)	0.86 (0.71, 1.04)	
0-10	16	0.02	721	0.03	0.79 (0.48, 1.30)	0.98 (0.59, 1.61)	

(b)

Proximity (km)	Cases		Control		Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	p-value for trend
	n	%	n	%			
>50	92,526	99.77	3,327,655	99.72	1.00 (Referent)	1.00 (Referent)	0.172
20-25	91	0.10	3,597	0.11	0.91 (0.74, 1.12)	0.93 (0.75, 1.14)	
15-20	72	0.08	3,430	0.10	0.76 (0.60, 0.95)	0.80 (0.63, 1.01)	
10-15	34	0.04	1,617	0.05	0.76 (0.54, 1.06)	1.00 (0.71, 1.41)	
5-10	14	0.02	605	0.02	0.83 (0.49, 1.41)	1.03 (0.60, 1.75)	
0-5	2	0.00	116	0.00	0.62 (0.15, 2.51)	0.72 (0.18, 2.94)	

(c)

Proximity (km)	Cases		Control		Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	p-value for trend
	n	%	n	%			
>50	92,526	99.55	3,327,655	99.46	1.00 (Referent)	1.00 (Referent)	0.122
20-40	299	0.32	12,297	0.37	0.87 (0.78, 0.98)	0.97 (0.86, 1.09)	
0-20	122	0.13	5,768	0.17	0.76 (0.64, 0.91)	0.87 (0.73, 1.04)	

[a]Adjusted for birth year, public health region, child's sex, maternal race/ethnicity, age, education, and gestational length.

6.4. Discussions and Conclusions

The insignificant Nuclear Facilities-LBW association found in the present study corroborated results from previous studies. In a study conducted in New York State over a 10-year period, the authors used four zones of 5-mile increments to categorize the proximity to a nuclear reactor. They concluded that LBW was not related to the proximity to the nuclear power plants (Mangones, Visintainer, and Brumberg 2013). The second group of sensitivity analysis in the present study (exposed groups: 0-5 km, 5-10 km, 10-15 km, 15-20 km, 20-25 km) utilized similar distance thresholds and found similar results as the New York State study.

A French study also concluded that there was no evidence of decreased mean birth weight when compared a "canton" (electoral ward) with nuclear facilities against a reference area without nuclear facilities (Slama et al. 2008). This French study used two separated regions as the study area and reference area, which was different from the proximity group design of the present study. However, if the present study only took into account the reference group (e.g. >50 km) and the proximity group that was closest to the nuclear facilities (e.g. 0-10 km), the design would be comparable to the French study. Both studies supported the conclusion of insignificant Nuclear Facilities-LBW association.

Wang et al.(2010) also summarized that residence in the vicinity of a nuclear power plant was not a significant factor of LBW (OR 1.04, 95% CI 0.79, 1.37) based on a study conducted in Taiwan over four years. This Taiwan study used distance threshold of 20 km to categorize the study population into "Plant-vicinity" and "Non plant-vicinity" group, which matched the parameter setting of sensitivity analysis III of the present study

(exposed groups: 0-20 km, 20-40 km). The odds ratio in the Taiwan study was 1.04 (95% CI 0.79, 1.37), which was also comparable to the ones in the present study (Table 6.5c).

The sensitivity analysis indicated that the proximity-based model in the present study was not sensitive to the choice of distance thresholds. However, if distance thresholds were too small, there would be very few cases/controls in some proximity groups. For example, the 0-5 km group in the sensitivity analysis II only had two LBW cases available. Under this circumstance, the confidence interval of the OR would be wide and the uncertainty of the OR would increase. Practically, the recommended distance thresholds should be relatively large in order to keep the number of cases and controls in each proximity group greater than five.

Although results from the present study did not identify any associations between maternal residential proximity to nuclear facilities and LBW in offspring, one should not conclude that there is no association at all. The reason is that the absence of evidence does not simply mean no information exists (evidence of absence) (Altman and Bland 1995). Therefore, although no evidence of the Nuclear Facilities-LBW association was found, one should not further infer that living closer to nuclear facilities would be risk-free or even healthier. Considering the serious effect of nuclear power plant accidents and widespread radiation exposure in population, studies searching for evidence of the Nuclear Facilities-LBW association have become very important; while existing studies did not prove such association, further studies should still be carried out when necessary (Altman and Bland 1995).

This study was not without limitations. First, there were only two nuclear power plants with four reactors in Texas, which limited the sample sizes in the exposed groups when calculating odds ratios. Three other operating research reactors in Texas were not included in this study because the power levels and fuel quantities at these facilities were very small when compared to large electrical power generation plants (U.S. NRC 2015b). Future studies may consider using larger research areas (e.g. the 48 continental United States) to include more nuclear facilities and LBW cases/controls in the exposed groups. Second, the study applied a proximity-based model that used a non-continuous function of distance as a proxy of ionizing radiation exposure to categorize the LBW cases/controls. Future research may consider using continuous functions (e.g. IDW) to improve the accuracy of exposure assessment. Third, this study categorized cases/controls into proximity groups using maternal residential addresses at delivery, assuming that maternal residential addresses were unchanged from conception to delivery. While it was true for most mothers, some mothers might have changed their residential locations during pregnancy (Canfield et al. 2006; Lupo et al. 2010), and the movement may have caused proximity group misclassifications for those mothers. However, since the movement tended to involve short distances, its effect on the proximity-based model might be minimal (Lupo et al. 2010).

This study has several strengths. First, it is the first attempt to investigate the Nuclear Facilities-LBW association in the southern United States. Its study area and study population were much larger than those in the previous studies. Second, the study also tested the sensitivity of proximity-based model to the distance thresholds, which was missing in most of existing studies. Last but not least, this study proposed a complete

methodology framework for study the Nuclear Facilities-LBW association. The framework can be conveniently applied to other study areas and health outcomes, and therefore can be used as a standardized protocol for the investigation of similar problems.

In this large population-based, case-control study, none of the exposed groups exhibits a statistically significant increase in LBW risk when compared to the reference group. These results were confirmed by sensitivity analysis based on proximity groups categorized by different distance thresholds. In summary, analysis results based on data in Texas during 1996-2008 suggest that there is no significant association between maternal residential proximity to nuclear facilities and LBW in offspring.

7. CONCLUSION

This chapter consists of three sections. Section 7.1 summarizes research findings and conclusions from the three studies of this dissertation. Section 7.2 outlines contributions of the dissertation to human environmental science and spatial epidemiology. Section 7.3 points out limitations of the research and suggests a number of future research directions.

7.1. Findings and Conclusions

The purpose of this research was to investigate environmental risk factors for LBW using geographic big data in Texas. More specifically, this research has three primary objectives: (1) to examine the association between maternal exposure to TRI chemicals and LBW in offspring; (2) to investigate the association between maternal exposure to TCEQ chemicals and LBW in offspring; (3) to examine the association between maternal residential proximity to nuclear facilities and LBW in offspring.

In order to achieve the first objective, the TRI Chemicals-LBW association study was conducted. This study identified ten chemicals that were most likely to be associated with LBW from all of the 449 TRI chemicals reported in Texas from 1996 to 2008 (Table 7.1). These ten chemicals are styrene, n-hexane, benzene, cumene, methyl isobutyl ketone, cyclohexane, zinc (fume or dust), o-xylene, propylene, and ethylene. In the case-control study, case-mothers were more likely to have a higher level of exposure to these ten chemicals than control-mothers, based on their residential locations and reported annual releases of chemicals from industry facilities. For four of these ten chemicals (styrene, o-xylene, n-hexane, and benzene), the risk of LBW increased monotonically

when the exposure intensities increased. The study also improved the accuracy of an exposure assessment model (EWPM) by using a geocomputational method for parameter calibration.

Table 7.1 Chemicals and critical exposure windows identified in the TRI Chemicals-LBW association study and the TCEQ Chemicals-LBW association study

Chemical Name	TRI Chemical	TCEQ Chemical	Adjusted OR[a] (95%CI)	Critical Exposure Windows[b] (time duration in days)
Methyl Isobutyl Ketone	x		1.06 (1.02, 1.10)	-
Cyclohexane	x		1.06 (1.03, 1.08)	-
Zinc (Fume Or Dust)	x		1.11 (1.07, 1.14)	-
Styrene	x		1.06 (1.04, 1.08)	-
o-Xylene	x		1.06 (1.03, 1.10)	-
n-Hexane	x		1.06 (1.05, 1.08)	-
Benzene	x		1.07 (1.05, 1.09)	-
Cumene	x		1.05 (1.04, 1.07)	-
Propylene	x		1.07 (1.04, 1.11)	-
Ethylene	x		1.06 (1.03, 1.09)	-
Benzaldehyde		x	2.66 (1.38, 5.12)	-288 ~ -198 (90)
			1.92 (1.09, 3.39)	102 ~ 192 (90)
4-methyl-1-pentene		x	1.96 (1.42, 2.70)	-192 ~ -162 (30)
			2.04 (1.14, 3.65)	198 ~ 288 (90)
Hexanaldehyde		x	2.25 (1.24, 4.07)	-360 ~ -270 (90)
Sum of PAMS target compounds		x	2.17 (1.17, 4.04)	-102 ~ -72 (30)
			2.46 (1.33, 4.55)	-54 ~ -24 (30)
			2.13 (1.15, 3.94)	126 ~ 216 (90)
m-Tolualdehyde		x	2.13 (1.13, 4.03)	-270 ~ -240 (30)
			2.31 (1.22, 4.40)	-180 ~ -150 (30)
n-Undecane		x	2.00 (1.19, 3.35)	198 ~ 288 (90)
p-Tolualdehyde		x	1.92 (1.02, 3.59)	-192 ~ -162 (30)
			1.88 (1.04, 3.39)	-162 ~ -132 (30)
Ethylene dibromide		x	1.97 (1.23, 3.14)	-294 ~ -204 (90)
n-Butane		x	1.26 (1.04, 1.52)	-144 ~ -114 (30)
			1.22 (1.01, 1.47)	-90 ~ -60 (30)
			1.79 (1.06, 3.02)	198 ~ 288 (90)
trans-Crotonaldehyde		x	2.12 (1.16, 3.86)	156 ~ 246 (90)

[a]Adjusted for child's sex, maternal race/ethnicity, age, education, and gestational length.
[b]days from date of conception.

The TCEQ Chemicals-LBW association study was conducted to achieve the second objective. From numerous combinations of the 367 TCEQ chemicals and various exposure windows, this study identified the top ten chemicals (benzaldehyde, 4-methyl-1-pentene, hexanaldehyde, sum of PAMS target compound, m-tolualdehyde, n-undecane, p-tolualdehyde, ethylene dibromide, n-butane, and trans-crotonaldehyde) and corresponding critical exposure windows that showed strongest effects on LBW in offspring (Table 7.1). Findings from the study suggested that case-mothers were more likely to be exposed to higher intensities of these ten chemicals within the critical exposure windows than control-mothers. The identified critical exposure windows in this study had flexible time durations (e.g. 30 days, 90 days) and starting times (e.g. before conception and after conception). Critical exposure windows after conception were found mainly in the second or third trimester of pregnancy. Critical exposure windows before conception were also identified in eight TCEQ chemicals, which indicated that mothers who were prepared for pregnancy should pay close attention to air quality in their living environment before conception. An additional contribution of this study is that it proposed a standardized protocol for interactively exploring critical exposure windows of air pollution-LBW associations based on the analysis of massive georeferenced air quality monitoring data.

The third objective was achieved through the Nuclear Facilities-LBW association study. In this large population-based, case-control study, none of the exposed groups showed a statistically significant increase in LBW risk when compared to the reference group. These results were confirmed by results from sensitivity analysis using different model parameters (distance thresholds) in exposure assessment. In summary, analysis

results based on data in Texas during 1996-2008 suggest that there is no significant association between maternal residential proximity to nuclear facilities and LBW in offspring.

7.2. Contributions

This dissertation has the following four contributions. First, this research investigated potential environmental risk factors for LBW which were scarcely examined previously, including TRI chemicals in the air, TCEQ chemicals in the air, and potential ionizing radiation from nuclear facilities.

Second, this dissertation had methodological contributions that can be used to support human environmental science research. The TRI Chemical-LBW association study improved the accuracy of an existing air pollution exposure assessment model (EWPM) by using a geocomputational method for parameter calibration. The TCEQ Chemical-LBW association study also proposed a new interactive method to investigate the air pollution-LBW associations using different exposure windows. The exposure windows in the new method had flexible starting times and time durations, and no prior knowledge about starting times and time durations was required to define these exposure windows.

Third, this dissertation examined if maternal exposure to chemicals before conception may be associated with LBW in offspring. Few reported studies have considered exposure windows covering a time period before conception. Results of this study revealed that LBW were associated with air pollution exposure not only during

pregnancy but also before conception, which enhanced existing knowledge about risk factors associated with LBW.

Last, but most importantly, this research has identified environmental risk factors of LBW, including ten TRI chemicals and ten TCEQ chemicals together with their corresponding critical exposure windows (Table 7.1). However, in previous studies, no significant effects were found for six of these ten TRI chemicals or any of these ten TCEQ chemicals. Based on the new findings from the dissertation, further epidemiological, biological, and toxicological studies can be conducted to explore the causal mechanisms of the associations. Moreover, these findings can raise public awareness of environmental risks, and help policy makers to establish better regulations. Hopefully, this research will contribute to the reduction of LBW rates.

7.3. Limitations and Future Work

This dissertation research has several limitations. First, in the TRI Chemical-LBW association study, only stacks of industrial facilities (point emission sources) were used as air emission sources in the analysis. Future research should include more emission source types (e.g., linear sources, area sources, and mobile sources) in the exposure modeling process in order to increase accuracy.

Second, edge effect might exist in the TRI Chemical-LBW association study because emission sources outside Texas were not considered. Therefore, the exposure intensities for mothers living in areas bordering other states and country might have been underestimated. Although these samples only accounted for a small percentage of the

total study population and results might have not been greatly affected, future studies should consider incorporating data from neighboring states or countries into the analysis.

Third, the uneven spatial distribution of the air quality monitoring sites might affect the results from the TRI Chemical-LBW association study and the TCEQ Chemical-LBW association study. As shown in Figure 3.2, most of the monitoring sites were concentrated in a few urban areas, and only few monitoring sites were located in suburban or rural areas. Consequently, air pollution conditions in those suburban or rural areas were not well represented by the air quality monitoring data used in the study. Accordingly, estimated exposure intensities might bear greater uncertainties in suburban or rural areas than that in urban areas. Additional studies can be conducted to understand and mitigate the effect of uneven geographic distribution of sampling points on exposure assessment.

A fourth limitation is related to the completeness of air quality monitoring data. Because the TCEQ Chemical-LBW association study used ambient monitoring data to estimate air pollution exposure, only chemicals with adequate monitoring records were used in the study, and chemicals whose monitoring records were incomplete were excluded from the study. This situation calls for a more complete collection of monitoring data in the future, especially for chemicals that have been found to be associated with LBW in previous studies but have had only few air quality monitoring records.

Last, in the Nuclear Facilities-LBW association study, only two nuclear facilities with four generators were available in Texas during the study time period. Therefore, the

sample sizes in exposed groups were limited, which might introduce uncertainties in the results. If birth certificate data from larger study areas (e.g. the 48 continental United States) can be obtained and integrated, similar study can be performed in the future in those larger areas to include more LBW cases/controls in exposed groups.

APPENDIX SECTION

APPENDIX A. CHEMICALS SHARED BY AIR EMISSION DATA AND AIR QUALITY MONITORING DATA

The table below lists calibrated parameters (effective distance *k* in EWPM) for the 78 chemicals shared by air emission data and air quality monitoring data.

Pollutants	CAS Number[a]	Sample Size	Spearman Rank Correlation Test		
			Optimal *k* (km)	Coefficient[b]	P-value (2-tailed)
Zinc (fume or dust)	7440666	24	7	0.754	<0.001
Propylene	115071	561	50	0.739	<0.001
Methyl tert-butyl ether	1634044	559	40	0.721	<0.001
1,3-butadiene	106990	597	33	0.671	<0.001
Ethylene	74851	561	50	0.653	<0.001
Cyclohexane	110827	597	6	0.629	<0.001
Arsenic	7440382	50	6	0.605	<0.001
Cadmium	7440439	24	7	0.561	0.004
Styrene	100425	597	10	0.555	<0.001
Naphthalene	91203	34	20	0.552	<0.001
Acrolein	107028	35	14	0.527	0.001
Chlorobenzene	108907	597	13	0.523	<0.001
N-hexane	110543	597	12	0.519	<0.001
Chloroform	67663	597	42	0.508	<0.001
Vinyl chloride	75014	597	11	0.508	<0.001
1,2-dichloroethane	107062	597	14	0.493	<0.001
Benzene	71432	597	12	0.490	<0.001
Dichloromethane	75092	597	16	0.442	<0.001
Chlorine	7782505	153	48	0.437	<0.001
Cumene	98828	597	16	0.437	<0.001
Chloromethane	74873	300	17	0.379	<0.001
Butyraldehyde	123728	151	44	0.348	<0.001
Nickel	7440020	21	23	0.323	0.153
Ethylbenzene	100414	597	12	0.315	<0.001
1,2-dichloropropane	78875	597	4	0.266	<0.001
Carbon tetrachloride	56235	596	15	0.263	<0.001
Trichloroethylene	79016	597	17	0.244	<0.001
Benzo(g,h,i)perylene	191242	69	10	0.242	0.046

Appendix A-Coutinued

Pollutants	CAS Number[a]	Sample Size	Spearman Rank Correlation Test		
			Optimal *k* (km)	Coefficient[b]	P-value (2-tailed)
Toluene	108883	597	13	0.236	<0.001
Tetrachloroethylene	127184	597	41	0.234	<0.001
Antimony	7440360	25	7	0.198	0.342
Mercury	7439976	153	50	0.191	0.018
Methyl isobutyl ketone	108101	253	3	0.186	0.003
1,2,4-trimethylbenzene	95636	597	3	0.182	<0.001
Bromine	7726956	153	45	0.178	0.027
Propionaldehyde	123386	65	33	0.174	0.166
O-xylene	95476	597	10	0.164	<0.001
1,1,2-trichloroethane	79005	597	6	0.160	<0.001
Isobutyraldehyde	78842	253	49	0.158	0.012
Lead	7439921	182	1	0.157	0.034
Vinylidene chloride	75354	597	14	0.155	<0.001
1,1,2,2-tetrachloroethane	79345	435	50	0.154	0.001
Formaldehyde	50000	66	43	0.150	0.230
1,1,1-trichloroethane	71556	592	50	0.107	0.009
Methyl ethyl ketone	78933	253	2	0.098	0.119
Chromium	7440473	20	26	0.090	0.705
1,2-dibromoethane	106934	435	9	0.082	0.086
Acetaldehyde	75070	66	50	0.046	0.714
Trichlorofluoromethane	75694	597	1	0.043	0.293
Ethylidene dichloride	75343	539	44	0.014	0.746
Chloroprene	126998	331	41	0.014	0.804
Beryllium	7440417	24	10	0.000	1.000
Bromomethane	74839	597	17	-0.011	0.788
Trans-1,3-dichloropropene	10061026	435	4	-0.019	0.688
Phenanthrene	85018	69	5	-0.039	0.750
Anthracene	120127	69	5	-0.170	0.161
Silver	7440224	24	10	-0.439	0.010
Alpha-hexachlorocyclohexane	319846	14	-	-	-
2,4,5-trichlorophenol	95954	14	-	-	-
2,4-dichlorophenol	120832	14	-	-	-
Isopropyl alcohol (manufacturing,strong-acid process only,no supplier)	67630	0	-	-	-

Appendix A-Coutinued

Pollutants	CAS Number[a]	Sample Size	Spearman Rank Correlation Test		
			Optimal *k* (km)	Coefficient[b]	P-value (2-tailed)
Aldrin	309002	14	-	-	-
Aluminum (fume or dust)	7429905	0	-	-	-
Barium	7440393	0	-	-	-
Carbon disulfide	75150	0	-	-	-
Cobalt	7440484	0	-	-	-
Copper	7440508	0	-	-	-
Crotonaldehyde	4170303	0	-	-	-
Dichlorodifluoromethane	75718	300	-	-	-
Heptachlor	76448	14	-	-	-
Lindane	58899	14	-	-	-
Manganese	7439965	0	-	-	-
Methoxychlor	72435	14	-	-	-
Ozone	10028156	0	-	-	-
Phosphorus (yellow or white)	7723140	0	-	-	-
Selenium	7782492	0	-	-	-
Vanadium (except when contained in an alloy)	7440622	0	-	-	-
N-butyl alcohol	71363	0	-	-	-

[a] A unique numerical identifier assigned by Chemical Abstracts Service (CAS) to every chemical substance described in the open scientific literature.
[b] Sorted by descending Spearman rank correlation coefficients.

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