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Maternal residential proximity to Toxics Release Inventory sites and preterm birth

By

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Master of Public Health

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B.A., University of California, Santa Barbara, 2006

Thesis Committee Chair: Matthew J. Strickland, PhD, MPH

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Abstract

Maternal residential proximity to Toxics Release Inventory sites and preterm birth

By Jamie S. White

This study was a secondary data analysis that examined the relationship between maternal residential proximity to Toxics Release Inventory (TRI) sites and preterm birth (PTB). A secondary outcome of interest was low birth weight (LBW). Study participants included 21,314 randomly selected singleton live births in Texas from 2001 to 2005 without congenital anomalies. Among total births, 8.53% were preterm and 5.82% were LBW, with and increased prevalence of PTB (11.31%) and LBW (9.58%) among non-Hispanic blacks. Geocoded maternal residence and ambient air pollution emission data from 977 TRI sites was used to determine exposure status. Using Geographic Information Systems (GIS), births with maternal residence within a one mile radius of a TRI site were classified as exposed. The effect of total emissions as well as specific chemical emissions or groups of chemical emissions on gestational age at birth and birth weight was explored. The prevalence of exposure varied from 1.14% to 13.54% depending on the exposure group of interest. Logistic and linear regression models controlling for several known risk factors of PTB and LBW were used to analyze the data in Statistical Analysis Software (SAS). Results for all regression models were generally consistent with no association. The null results may be partially attributable to non-differential exposure misclassification. This study found no evidence of a relationship between maternal residential proximity to TRI sites and PTB or LBW for any chemical exposure groups of interest. There was no evidence of a dose-response relationship for any exposure of interest. There was also no significant or consistent evidence of effect modification by race/ethnicity.

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Introduction

Preterm birth (PTB) and low birth weight (LBW) in the United States

Epidemiology of preterm birth and low birth weight

In 2006, the nation's preterm births numbered over half a million. The percentage of infants born preterm rose to 12.8% in 2006, a 25% increase since 1990[1]. After this long-term steady trend there was a two-year consecutive decline in PTBs in the United States, to 12.3% in 2008[2, 3]. Most of the increase in PTBs from 1990 to 2006 was among infants born late preterm (34 to 36 weeks gestation) [1, 4]. In 2006, 71.4% of PTBs were late preterm, 12.6% were moderate preterm (32-34 weeks gestation), 10.0% were very preterm (28-31 weeks gestation) and 5.9% were extremely preterm (<28 weeks gestation)[1]. Singleton PTBs rose to 11.1% of total births in 2006, a 14% increase from 1990[1]. By 2008, singleton PTBs decreased slightly to 10.9% of total births[2]. PTBs in Texas were slightly higher than in the US in both 2006 and 2008, at 13.7% and 13.3% respectively[1, 2]. In 2008, 11.9% of singleton births in Texas were preterm. PTBs in Texas numbered 53,923 infants in 2008, accounting for over 10% of the number of PTBs in the US (523, 033 infants)[2].

The percentage of infants born low birth weight (less than 2,500 grams) also rose to the highest level in four decades in 2006; 8.3% of births were LBW, a 19% increase from 1990[5]. Singleton LBW infants increased 10% from 1990 to 2006[1]. The percentage of LBW infants remained stable the next two years at 8.2%[2, 3]. The percentage of live births that were LBW in Texas was also slightly higher than in the nation, at 8.4% in both 2006 and 2008[2].

Risk factors for preterm birth and low birth weight

Many maternal and infant risk factors or characteristics have been associated with spontaneous preterm birth and low birth weight in infants without congenital malformations. These include multiple gestation, maternal age, maternal parity, diabetes mellitus, tobacco use during pregnancy, fetal gender, adequate prenatal care, marital status, and socioeconomic status.

Multiple gestation. Twins and higher level multiples are more likely than singletons to be born preterm or LBW. In the US in 2008, 61.3% of multiple births were born premature compared to 10.9% of singletons, and 59.0% of multiple births were born LBW compared to 6.4% of singletons. In Texas in 2008, 65.0% of multiple births were born premature compared to 11.9% of singleton births and 62.5% of multiple births were LBW compared to 6.7% of singleton births[6].

Maternal age. The relationship between maternal age and PTB or LBW is non-linear; a U-shaped distribution is observed in the relationship, with the youngest and oldest mothers at highest risk for PTB or LBW. In the US in 2008, mothers over age 40 and teen mothers had the highest rates of preterm birth and low birth weight (see Table 1 below)[6]. Older mothers may be at increased risk of PTB and LBW due to higher prevalence of co-morbidities and multiple births, and use of assisted reproductive technologies (ART)[7]. Teen mothers may be at increased risk of PTB and LBW due to biologic immaturity of the female reproductive tract, behavioral risk factors, and lower socioeconomic status[8]. In 2008, the rate of teen births decreased 2% to 41.5 per 1,000 whereas the rate of birth for women 40-44 increased to the highest reported in over 40 years[2].

Table 1: Percentage of live births preterm and LBW by maternal age, United States and Texas, 2008						
Outcome	Population	Maternal age in years				
		<20	20-29	30-39	≥40	All ages
PTB	US	14.5%	12.0%	12.6%	17.1%	12.3%
	Texas	14.9%	12.8%	13.9%	18.6%	13.3%
LBW	US	9.9%	7.8%	8.0%	11.6%	8.2%
	Texas	9.6%	8.0%	8.5%	12.3%	8.4%

Maternal parity. Previous studies indicate that in general, nulliparous women are at higher risk for PTB and LBW than parous women. There may be some interaction between age and parity, with teen multiparous and older nulliparous women at greatest risk for PTB and LBW[9, 10]. Socioeconomic factors and pregnancy spacing associated with multiparous teens may account for this anomaly[9]. Miranda et al suggest that this observed difference in PTB and LBW between nulliparous and parous women is partially attributable to higher-risk women not having a subsequent live birth, either by choice or due to fecundity differences[11].

Diabetes mellitus. Previous research has shown that women with pre-gestational diabetes mellitus are at an increased risk for PTB, but also large for gestational age birthweight[12]. Hedderson et al. found an increasing risk of preterm labor with increasing levels of pregnancy glycemia[13].

Tobacco use during pregnancy. Tobacco use during pregnancy is a well-established risk for PTB and LBW, with a clear dose-response relationship between amount of tobacco consumed and risk of adverse birth outcomes[14, 15]. It is one of the most commonly abused drugs during pregnancy, and is more likely than cocaine or marijuana use during pregnancy to result in PTB or LBW[16]. Mohsin and Jaludin found that smoking cessation during pregnancy among women who previously had a PTB infant significantly decreased risk of subsequent preterm labor[17].

Fetal gender. Male fetuses are more likely than female fetuses to be born premature. The mechanism for this phenomenon is not well understood, but it has been hypothesized that relative greater weight at lower gestational age or gender-associated factors that predispose mothers to reproductive tract infection during pregnancy increase risk of preterm birth for male fetuses[18]. Cooperstock and Campbell found a 7.2% excess of males among white singleton preterm births, approximately evenly distributed over 20-37 weeks gestation. However, there was only a 2.8% excess of males among black singleton preterm births, suggesting that the mechanism for preterm birth among blacks may be independent of fetal gender[19].

Adequate prenatal care. Prenatal care is generally accepted as protective against adverse birth outcomes including PTB and LBW. The timing of prenatal care may be vital to effectively addressing the underlying causes of these adverse birth outcomes, with early (first trimester) or even pre-conception care providing the most protection. While the utilization of prenatal care had been correlated with birth outcomes, there is limited research on how the content of care affects birth outcomes[20]. Early screening and treatment for genital tract infections may be one aspect prenatal care that prevent some PTB and LBW deliveries[21].

Marital status. Previous research has shown that unmarried mothers in all age groups are at higher risk of PTB relative to married mothers[22]. This pattern may be indicative of level of paternal involvement associated with marital status. The presence of father's name on a birth certificate is highly correlated with marital status. However, no father's name on a birth certificate may be a better predictor of PTB and LBW than marital status at time of birth[23]. Zeitlin et al. found that the association between marital

status and preterm birth is mediated by the marital practices in a population, with unmarried mothers at higher risk of PTB if living in populations where a higher percentage of births occur to married women[24].

Socioeconomic status. A systematic literature review of the relationship between low socioeconomic status and adverse birth outcomes including PTB and LBW found that socioeconomic disadvantage was consistently associated with increased risk[25]. The same review noted that many studies observed racial/ethnic differences in the effect of socioeconomic measures.

Racial/ethnic disparities in preterm birth and low birth weight

Racial disparities in birth outcomes are striking, particularly for non-Hispanic blacks or African Americans. It has been hypothesized that the social stress of racism and the social inequality it creates may be an underlying determinant of PTB and LBW[26]. An approach called the life-course perspective is increasingly used in reproductive epidemiology to understand racial/ethnic disparities in a social and structural context. One focus of the life-course perspective is how experiences of racism over the course of a lifetime can shape reproductive health outcomes, including PTB and LBW, later in life and potentially across generations[27]. Racial segregation is an example of a possible social and structural determinant of health outcomes. Kramer et al. found that in a metropolitan Atlanta population African American women living in isolation segregation have an excess risk of PTB, while white women living in isolation segregation have no excess risk of PTB[28]. They suggest that individual socioeconomic status and metropolitan crime only partially explains this excess risk. African American may be especially vulnerable to other risk factors of PTB and LBW compared to other

racial/ethnic groups. Hitti et al. found that lower genital tract infection was significantly associated with PTB and LBW among African American but not among other racial ethnic groups[29].

Birth outcomes among Hispanics are more comparable to non-Hispanic whites, or disparities are less pronounced than would be expected given average socioeconomic and educational status, an epidemiologic phenomenon called the 'Hispanic birth paradox'[30]. It has been hypothesizes that this paradox is attributable to the 'migrant effect' in which Foreign-born Hispanics are generally healthier than their US-born counterparts[31].

The prevalence of premature birth in 2008 by maternal race/ethnicity for non-Hispanic blacks or African Americans and non-Hispanic whites were 18.1% and 12.2% respectively, compared to 11.4% for non-Hispanic whites. The prevalence of LBW for these racial/ethnic groups were 13.9% and 7.0% respectively, compared to 7.3% for non-Hispanic whites[2]. These disparities highlight the need for further research on the etiology of adverse birth outcomes.

Seasonality of preterm birth and low birth weight

Previous literature has documented seasonal variability in preterm birth and low birth weight. This effect may be largely due to seasonal differences in the demographic composition of pregnant women. Different racial/ethnic groups vary in seasonal patterns of conception date[32].

Etiology of preterm birth and low birth weight

The etiology of preterm birth and low birth weight is poorly understood and believed to be multi-factorial. Medical conditions of the mother or fetus, genetic influences, environmental exposures, infertility treatments, and behavioral and socioeconomic factors have all been linked to PTB and LBW[33]. Additional research on

the etiology of PTB and LBW may provide insight into the biological mechanisms underlying these adverse outcomes.

Approximately two-thirds of all singleton PTBs are spontaneous, often of unknown cause, and approximately one third are the medically indicated cesarean delivery[34]. Cesarean delivery rose to 32.2% in 2008[2]. There is concern this increase is partially attributable to medically indicated cesarean delivery that is not truly necessary. Patient and physician awareness of the risks associated with PTB and LBW may influence decisions regarding cesarean delivery when weighed against the risks of continued pregnancy.

Among singleton births, medically indicated PTBs increased from 2.6% in 1989 to 3.8% in 2000, but these overall trends may conceal patterns within subpopulations[35]. The increase in PTB among non-Hispanic whites was largely the result of a 55% increase in medically indicated preterm births, whereas the decrease among non-Hispanic blacks was due to a 27% decrease in spontaneous preterm birth and 37% decrease in ruptured membranes[35].

Morbidity and mortality associated with preterm birth and low birth weight

Preterm birth and low birth weight are intractable public health problems with serious medical, social and economic costs. Worldwide, 28% of all neonatal deaths (deaths within the first seven days of life) not related to congenital malformations are attributable to PTB[36]. PTB is the leading cause of neonatal mortality and a major cause of pediatric morbidity in the United States. Over 100,000 PTBs resulted in serious medical complications and over 4,800 infant deaths in the US in 2006[1]. While babies born before the 34th week of gestation are at the greatest risk for increased mortality and

morbidity, it is generally recognized that later preterm infants are less healthy than full-term infants. Preterm babies are more likely than full-term babies to experience medical complications including breathing problems, jaundice, anemia and infections. LBW and PTB have also been associated with lifelong chronic conditions including mental retardation, learning and behavioral problems, vision and hearing loss, cerebral palsy, hypertension and diabetes[37]. Recent studies suggest that VPTB and LBW infants may be at increased risk of developing symptoms of autism and be associated with increased severity of symptoms in individuals with autism spectrum disorders[38-40].

Social consequences of preterm birth and low birth weight

Preterm birth and LBW affect social as well as health issues in the United States. Prematurity and LBW are associated with a reduced likelihood of completing high school and attending college[41]. Lipkind et al. found a positive linear relationship between gestational age at birth and third-grade standardized math and English test scores[42].

Economic burden of preterm birth and low birth weight

Preterm birth and low birth weight also have a substantial economic impact in the United States. The March of Dimes PeriStats estimates the cost of PTB in the United States exceeded $26.2 billion in 2005, in terms of medical and educational expenses and associated lost productivity. A cross-sectional study of PTB/LBW-associated costs for infant hospitalizations using the 2001 National Inpatient Sample found that PTB/LBW accounted for 47% of all infant costs for only 8% of all infant admissions, and 27% of all pediatric hospital costs for six percent of all pediatric admissions.[43] The same study found the average cost of hospitalization for LBW and very low birth weight were $20,600 and $52,300 respectively. Even small increases in birth weight and gestational

age at birth have been shown to decrease cost of initial hospital stay and the number of re-hospitalizations in the first year of life.[44]

Healthy People objectives and Health Babies campaigns

Reducing prevalence of preterm birth and low birth weight in the United States were objectives of *Healthy People 2010* (HP2010) and are currently objectives of *Healthy People 2020* (HP2020). The target setting method for these objectives in HP2010 was listed as "better than the best," with a target of reducing both PTB and LBW to 7.6%[45, 46]. These HP2010 objectives remain unmet despite advancements in technology and treatments over the past decade. The Healthy People 2020 objectives are less ambitious, with target methods based on 10% and 5% improvements for PTB and LBW prevalence respectively. Target goals for these HP2020 objectives are to reduce PTB to 11.4% and LBW to 7.8%. More specific HP2010 and 2020 objectives and corresponding baseline prevalence used to set them are listed in Table 2 below.

Table 2: Healthy People 2010 and 2020 preterm birth (PTB) and low birth weight (LBW) objectives

Birth Outcome		Healthy People 2010		Healthy People 2020	
		Baseline (US 1998)	2010 Objective	Baseline (US 2007)	2020 Objective
PTB	Total <37 weeks	11.6%	7.6%	12.7%	11.4%
	34-36 weeks	9.6%	6.4%	9%	8.1%
	32-33 weeks			1.6%	1.4%
	<32 weeks	2.0%	1.1%	2%	1.8%
LBW	Total < 2,500 grams	7.6%	7.6%	8.2%	7.8%
	<1,500 grams	1.4%	0.9%	1.5%	1.4%

The US only achieved a "D" on the March of Dimes Premature Birth Report Card in 2009 for the second consecutive year and Texas received an "F"[47]. In response to increasing PTB in the United States of the past two decades, the March of Dimes and the Johnson & Johnson Pediatric Institute collaborated with the Kentucky Department of

Public Health to pilot *Healthy Babies are Worth the Wait* (HBWW), a preterm birth prevention initiative, from 2007 to 2009[48]. The goal of HBWW is to raise awareness among providers and patients of the consequences of preterm birth in the hopes of preventing caesarean delivery without medication indication. A new HBWW collaborative, the *Healthy Texas Babies Initiative*, has started in Texas based on the success of the initiative in Kentucky.

Toxics Release Sites

Toxics Release Inventory Program

The Environmental Protection Agency (EPA) is required under the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) to make chemical release information accessible to the public. The EPA disseminates this information in a national database called Toxics Release Inventory (TRI) and maintains a searchable online database that can aggregate data by chemical, industry, emission quantity and various regional indicators. Facilities subject to the reporting requirements of EPCRA are required to submit annual reports for each eligible chemical to the EPA and to the state or tribal government where the facility is located. For each TRI-listed chemical released in excess of certain thresholds, the facility must submit a Form R, which provides detailed information about the chemical, including amount released to air, land, water, underground injection, or transferred off-site.

Environmental factors including residential proximity to sites reporting toxic releases may provide insight into the causes of increasing prematurity and low birth weight in the United States. In 2005, 23,461 facilities reported to EPA's Toxics Release Inventory Program. These facilities reported 4.34 billion pounds of on-site and off-site disposal or other releases of about 650 toxic chemicals. This widespread and potentially

severe exposure justifies further investigation into possible associations with adverse birth outcomes including prematurity and LBW.

Toxic sites and social justice

Congress passed the EPCRA in response to the Bhopal Disaster, in which thousands of deaths resulted from the accidental release of the toxic gas methyl isocyanate (MIC) at a Union Carbide facility in Bhopal, India. Environmental right-to-know policies such as the establishment of the TRI database may enhance or possibly replace some traditional command-and-control policies; concerns over liability, negative publicity and associated costs may spur a corporation to voluntarily improve environmental performance [49]. Similarly, corporations may be motivated to voluntarily improve environmental performance to prevent public backlash when inequalities in pollution exposures between racial/ethnic and socioeconomic groups exist.

Under the TRI Burden Reduction Rule in 1995, the EPA began allowing facilities to submit two-page Certification Statement (Form A) instead of Form R for chemicals that are not persistent, bioaccumulative toxics (PBT), provided a facility does not release more than 500 total pounds, and does not manufacture, process, or use more than one million pounds of the chemical. Form A does not contain any of the Form R details about how much of the chemical is used, released, or managed as waste. The EPA environmental justice analysis of the TRI Burden Reduction Rule concluded that it doesn't disproportionately affect minority and low-income populations. However, one study concludes that facilities eligible to file Form A are more likely to be located in neighborhoods with a high proportion of minority and low-income residents compared to those still required to submit Form R[50]. The authors argue that the reduction rule

minimizes the leverage of citizens to demand reductions in industrial releases and makes assessment of health risks in different communities more difficult and less complete.

Ambient air pollution and adverse birth outcomes

Previous studies have associated prenatal exposure to environmental pollutants with adverse birth outcomes. Specifically, there is a growing body of scientific evidence suggesting ambient levels of air pollution are associated with a slight to moderate increase in risk of preterm birth. Several previous studies from varying geographic locations have shown a statistically significant increase in relative risk (ranging from 1.06-1.27) for PTB associated with an elevated ambient PM_{10} exposure during at least one gestational window[51-54] or with ambient $PM_{2.5}$ exposure during at least one gestational window[55-57]. Other studies have shown slightly increased relative risks but failed to achieve statistical significance for any gestational window considered[32, 58]. Table 3 below summarizes select results from these studies. These results provide compelling evidence for a weak association between particulate matter exposure and PTB. However, the critical periods of gestational exposure are unclear and more research is needed to establish dose-response relationships. Preliminary studies support the use of further spatial analysis in examining the relationship between ambient air pollution and adverse birth outcomes.

Previous studies have investigated various adverse birth outcomes associated with proximity to waste sites. Maternal residential proximity to toxic waste sites has been associated with conotruncal heart defects[59] and neural tube defects[60]. Previous studies have also associated air pollution from municipal waste incinerators with altered birth sex ratios and lethal congenital anomalies[61, 62]. However, the literature is lacking research

specifically investigating PTB and LBW associated with ambient air pollution emissions from Toxics Release Inventory sites.

The mechanism by which ambient air pollution may cause PTB or LBW is uncertain, but several hypotheses have been suggested. There is evidence that inflammatory pathways and implantation errors in pregnancy have a role in gestational age and weight at birth[63]. Particulate matter may cause oxidative stress, pulmonary and placental inflammation, blood coagulation, endothelial dysfunction, or hemodynamic responses which could lead to preterm birth or low birth weight[64]. Exposure to ambient air pollution may increase maternal susceptibility to infections during the weeks before birth[54]. Other unmeasured toxics correlated with particulate matter including polyacyclic aromatic hydrocarbons (PAHs) and metals may cause fetal oxidative stress resulting in preterm birth or low birth weight[56]. Our limited understanding of the pathophysiology of PTB and LBW supports the need for more research. Exploratory research on more specific types of ambient air pollution exposures including metals and PAHs are warranted.

Table 3: Gestational exposure to ambient particulate matter and preterm birth

Study	Location	Population size	Study Design	Mean or median exposure (PM size)	Exposure level	Gestational window of exposure	Adjusted measure of effect (95% CI)
Brauer et al. (2008)	Vancouver, Canada	70,249	Retrospective Cohort	Mean = 5.3 μg/m^3 ($PM_{2.5}$)	1 μg/m^3 increase	Total gestation	OR = 1.06 (1.01-1.11)
				Mean = 12.7 μg/m^3 (PM_{10})			NA
Darrow et al. (2009)	Metropolitan Atlanta, GA, USA	476,489 Within 4-mile radius of monitor	Time-series	Mean = 9.1 μg/m^3 ($PM_{2.5}$)		First month	RR = 0.99 (0.93-1.05)
						6-week lag	RR = 1.05 (0.96-1.16)
				Mean = 23.9 μg/m^3 (PM_{10})		First month	RR = 1.07 (0.99-1.17)
						6-week lag	RR = 1.01 (0.90-1.14)
Hansen et al. (2006)	Brisbane, Australia	28,200	Cross-sectional	Mean = 19.6 μg/m^3 (PM_{10})	Interquartile range increase	1st trimester	OR = 1.15 (1.06-1.25)
						3rd trimester	OR = 1.04 (0.92-1.16)
Huynh et al . (2006)	California, USA	10,373 cases, 32,019 controls	Case-control	Mean (total gestation) = 17.5 μg/m^3 cases, 18.0 μg/m^3 controls ($PM_{2.5}$)	Quartile (highest vs. lowest quartile shown)	Total gestation	OR = 1.15 (1.07, 1.24)
						First month	OR = 1.21 (1.12, 1.30)
						Last two weeks	OR = 1.17 (1.09, 1.27)
					10 μg/m^3 increase	Total gestation	OR = 1.15 (1.15, 1.16)
						First month	OR = 1.13 (1.12, 1.13)
						Last two weeks	OR = 1.06 (1.05, 1.06)
Kim et al. (2007)	Seoul, Korea	1,514	Prospective cohort	88.7-89.7 μg/m^3 (PM_{10})	10 μg/m^3 increase	1st trimester	RR = 1.1 (1.0-1.2)
						2nd trimester	RR = 1.1 (1.0-1.2)
						3rd trimester	RR = 1.1 (1.0-1.1)
Leem et al. (2006)	Incheon, Korea	52,113	Cross-sectional	NA (PM_{10})	Highest vs. lowest quartile	1st trimester	OR = 1.27 (1.04-1.56)
						3rd trimester	OR = 1.09 (0.91-1.30)
Ritz et al. (2000)	Southern California, USA	95,518	Cohort	49.3 μg/m^3 (PM_{10})	50 μg/m^3 increase	First month	RR = 1.09 (0.99-1.20)
				47.5 μg/m^3 (PM_{10})		Last 6 weeks	RR = 1.15 (1.03-1.29)
Ritz et al. (2007)	Los Angeles, California, USA	2,543	Nested case-control	20.01 μg/m^3 ($PM_{2.5}$)	Evenly-spaced intervals (>21.36 μg/m^3 vs. <=18.63 μg/m^3 shown)	1st trimester	OR = 1.29 (1.00-1.67)
Sagiv et al (2005)	Pennsylvania, USA	187,997	Time-series	25.3 μg/m^3 (PM_{10})	50 μg/m^3 increase	Last 6 weeks	RR = 1.07 (0.98-1.18)
					Quartile (highest vs. lowest quartile shown)		RR=1.03 (0.99-1.14)
Wilhelm and Ritz (2005)	Southern California, USA	106,483 Within 2 mile radius of monitor	Retrospective Cohort	21.0-21.9 μg/m^3 ($PM_{2.5}$)	10 μg/m^3 increase	1st trimester	RR = 0.73 (0.67-0.80)
						Last 6 weeks	RR = 1.10 (1.00-1.21)
				39.1-42.2 μg/m^3 (PM_{10})		1st trimester	RR= 0.99 (0.96-1.01)
						Last 6 weeks	RR = 1.02 (0.99-1.04)

Aims of current research

The research hypothesis for this study is that maternal residential proximity to Toxics Release Inventory (TRI) sites is associated with preterm birth and low birth weight. It is further hypothesized that there is effect modification by race/ethnicity, with non-Hispanic blacks at highest risk of PTB and LBW. An additional objective of this study is to explore the effect of specific chemicals or groups on chemicals on gestational age at birth and birth weight. Previous research on the high medical, social and economic costs of adverse birth outcomes and the trend of increasing PTB and LBW in the United States, coupled with the widespread and potentially severe exposures to ambient pollutants from TRI sites provide rationalization for this study. We will use geographic information systems (GIS) to approximate exposure to ambient pollutants from TRI sites. We will then use epidemiologic modeling to assess the relationship between exposure status with PTB and LBW among a population of pregnant women residing in Texas.

Materials and Methods

Study population. This study was a secondary data analysis. The study population was comprised of the population-based controls from a previous research study on the epidemiology and regional variation of clubfoot[65]. These participants were randomly selected, without major congenital anomalies, and limited to live births in Texas from a five year period beginning in 2001 and ending in 2005. Cases of clubfoot were removed from the dataset and were excluded from analysis in this study. Due to the availability of geocoded data and the preservation of internal validity, only participants who resided in Texas at the time of birth were included in analysis. Birth records for the study population were obtained from data previously collected by a Texas state surveillance program with permission from the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention.

Birth data. Each observation contained data for geocoded maternal residence, mother's characteristics (age, race/ethnicity, education, marital status, tobacco use during pregnancy, parity, gravidity), child's sex, gestational age in weeks, birth weight, birth month and year, breech presentation at birth and prenatal care. Births in 2005 contained additional data for maternal diabetes, method of payment and Medicaid status. Thirty-two triplet and 626 twin births were excluded from analysis. The final analysis included 21,314 singleton live births.

Air pollution data. Geocoded Toxics Release Inventory (TRI) sites in Texas were identified from the US EPA's publically available TRI.net data engine. TRI sites within one mile of the Texas border in neighboring states were considered for analysis but were not within one mile of any maternal residence. Emissions data for sites within one mile of the Texas border in Mexico were unavailable. TRI site data included point source air

emissions in pounds for total ambient air pollution; hazardous air pollutants (HAPs); ten chemicals identified by EPA's TRI-CHIP database as reproductive hazardous air pollutants (nickel, beryllium, cadmium, copper, zinc, mercury, selenium, barium, arsenic, formaldehyde); metals and metal compounds; polycyclic aromatic hydrocarbons (PAHs); and benzene for years 2000 through 2005. TRI sites reporting zero point source air emissions for an exposure group of interest were excluded from the respective analysis. The number of included TRI sites varied by exposure year with the highest number of sites in a single year at 993 for total emissions, 897 for HAPs, 347 for TRI-CHIP 10, 395 for metals, 107 for PAHs and 127 for benzene. TRI sites were categorized as low, medium, or high exposure level based on the distribution of pounds of point sources air emissions for each exposure group of interest.

Exposure status. We used the date when each fetus reached gestational age 20 weeks to determine the year of ambient air pollution exposure to assign each infant. Timing of exposure ranged over a six-year period beginning in 2000 and ending in 2005 due to some years of exposure occurring in the calendar year prior to the year of birth. For each exposure of interest, observations were classified as exposed if maternal residence was within a one mile radius of any TRI site emitting point source air emissions for each respective exposure group of interest during the exposure year. Observations were classified as unexposed if maternal residence was *not* within a one mile radius of any TRI site emitting point source air emissions for each respective exposure group of interest during the exposure year. ESRI's ArcMap geographic information system (GIS) software was used to identify maternal residences within a one mile radius of TRI sites. For additional analysis, exposure status for observations within

one mile of a TRI site was refined to be high, medium or low based on the emissions level of the TRI site. Maternal residences located within one mile of two or more TRI sites in different exposure level categories were categorized in the higher of the two exposure level categories.

Modeling design. We created linear models with gestational age and birth weight as continuous variables. We also created logistic models comparing preterm birth (<37 weeks gestation) with term birth (≥37 weeks gestation), and comparing low birth weight (<2,500g) with non-low birth weight (≥2,500g).

Covariates were based on available data and previous literature identifying potential risk factors for preterm birth and low birth weight. We adjusted for mother's age in years (continuous); any tobacco use during pregnancy (dichotomous); maternal education in years (<12, 12, 13-15, or ≥16); parity (dichotomous); prenatal care in first trimester (dichotomous); sex of child (dichotomous); maternal marital status (dichotomous) and mother's race/ethnicity (categorical). Mother's age was found to have a non-linear relationship with the outcome variables, with increased risks observed among youngest and oldest age groups. A parameter for maternal age-squared was added to the model to allow for this non-linear relationship. Mother's race/ethnicity was indicated as non-Hispanic white, non-Hispanic black, Hispanic, and other. The 'other' category included Asian, Native American and unknown or mixed race/ethnicity. Additional interaction models using indicator variables for race/ethnicity were applied to explore potential effect modification. Gravidity was excluded as a covariate due to high collinearity with parity. Table 4 below shows the epidemiologic models used for analysis and Table 5 provides variable descriptions and levels of measurement for these models.

Dose-response. We also created logistic models using indicator variables for each level of exposure to evaluate potential dose-response relationships.

2005 sub-analysis. A sub-analysis using data from 2005 births only was conducted to evaluate the effect of additionally available potential confounders. We created logistic models that included additional covariates maternal diabetes (dichotomous) and Medicaid status (dichotomous). Data for maternal diabetes and Medicaid status were not missing for any 2005 births.

Calendar year. The prevalence of preterm birth and low birth weight were tabulated by calendar year of birth (year of outcome) to examine trends over time in the study sample. The no-interaction logistic models were expanded to include indicator variables for year of exposure to further explore this trend.

Seasonality. The prevalence of preterm birth and low birth weight were tabulated by month of birth to explore seasonal variability in birth weight and preterm delivery. However, birth month was not considered a confounder and was excluded from the final models.

Missing data. No outcome or exposure data were missing for any observations. Missing covariate data were minimal. No data were missing for prenatal care, tobacco use during pregnancy, child's sex or maternal marital status. Twenty-six observations missing maternal race/ethnicity were combined with the 'other' race category. Nineteen observations were missing for marital status (0.09%), 243 for mother's education (1.15%), and 647 for parity (3.04%). These missing observations were excluded from final analysis. Additional models were run with missing data for parity reassigned as parous and again as non-parous to evaluate potential bias. Similarly, additional models

were run with missing data for mother's education reassigned in the lowest educational category and again in the highest educational category to evaluate potential bias.

Table 4: Epidemiologic models	
Model 1: No interaction model	$OUTCOME = \alpha + \beta_1*EXPOSURE + \beta_2*MOTHAGE + \beta_3*(MOTHAGE^2) + \beta_4 MOTHED + \beta_5 PAR + \beta_6*CARE + \beta_7*SMOKE + \beta_8*MALE + \beta_9 MARRY + \beta_{10}*RACE$
Model 2: No interaction model with ordinal levels of exposure (unexposed = referent)	$OUTCOME = \alpha + \beta_1*ELOW + \beta_2*EMED + \beta_3*EHIGH + \beta_4*MOTHAGE + \beta_5*(MOTHAGE^2) + \beta_6*MOTHED + \beta_7*PAR + \beta_8*CARE + \beta_9*SMOKE + \beta_{10}*MALE + \beta_{11}*MARRY + \beta_{12}*RACE$
Model 3: Interaction by race/ethnicity (white = referent)	$OUTCOME = \alpha + \beta_1*EXPOSURE + \beta_2*MOTHAGE + \beta_3*(MOTHAGE^2) + \beta_4 MOTHED + \beta_5 PAR + \beta_6*CARE + \beta_7*SMOKE + \beta_8*MALE + \beta_9 MARRY + \beta_{10}*BLACK + \beta_{11}*HISP + \beta_{12}*OTHER + \beta_{13}*BLACK*EXPOSURE + \beta_{14}*HISP*EXPOSURE$
Model 4: No interaction model with indicators for exposure year (2000=referent)	$OUTCOME = \alpha + \beta_1*EXPOSURE + \beta_2*MOTHAGE + \beta_3*(MOTHAGE^2) + \beta_4 MOTHED + \beta_5 PAR + \beta_6*CARE + \beta_7*SMOKE + \beta_8*MALE + \beta_9 MARRY + \beta_{10}*RACE + \beta_{11}*Y1 + \beta_{12}*Y2 + \beta_{13}*Y3 + \beta_{14}*Y4 + \beta_{15}*Y5$

Table 5: Variable descriptions and levels of measurement		
Variable	**Description**	**Levels**
OUTCOME	Outcome of interest; either indicator of preterm birth (<37 weeks gestation) or low birth weight	0=no event 1=event
EXPOSURE	Indicator for residential proximity within one mile to TRI site with air pollutant(s) of interest (either total air emissions, HAPs, TRI-CHIP 10, metals, PACs or benzene)	0=maternal residence not within one mile of TRI site of interest at time of delivery 1=maternal residence within one mile of TRI site of interest at time of delivery
ELOW	Indicator for residential proximity within one mile to a TRI site classified as low exposure for air pollutant(s) of interest	0=maternal residence not within one mile of low-exposure TRI site of interest at time of delivery 1=maternal residence within one mile of low-exposure TRI site of interest at time of delivery
EMED	Indicator for residential proximity within one mile to a TRI site classified as low exposure for air pollutant(s) of interest	0=maternal residence not within one mile of medium-exposure TRI site of interest at time of delivery 1=maternal residence within one mile of medium-exposure TRI site of interest at time of delivery

EHIGH	Indicator for residential proximity within one mile to a TRI site classified as low exposure for air pollutant(s) of interest	0=maternal residence not within one mile of high-exposure TRI site of interest at time of delivery 1=maternal residence within one mile of high-exposure TRI site of interest at time of delivery
MOTHAGE	Mother's age in years	Continuous (12-54)
$MOTHAGE^2$	Square of mother's age	Continuous (>0)
MOTHED	Ordinal variable for mother's highest level of education	1 = <12 yrs. (no diploma) 2 = 12 yrs. (diploma or GED) 3 = 13-15 yrs (some college/associates) 4 = ≥16 yrs. (college graduate/above)
PAR	Dichotomous indicator for parity	0 = No previous births 1= One or more previous births
CARE	Dichotomous indicator for prenatal care in the first trimester of pregnancy	0 = Prenatal care after 1st trimester or no prenatal care 1 = Prenatal care in 1st trimester
SMOKE	Dichotomous variable to indicate maternal cigarette smoking during pregnancy	0 = no smoking 1 = at least 1 cigarette smoked per day during pregnancy
MALE	Dichotomous variable to indicate male sex	0 = female infant 1 = male infant
MARRY	Dichotomous variable to indicate maternal marital status	0 = not married 1 = married
RACE	Categorical variable for race/ethnicity	0 = Other 1 = Black, non-Hispanic 2 = Hispanic 3 = White, non-Hispanic
BLACK	Dichotomous variable to indicate non-Hispanic black race/ethnicity	0 = not black, non-Hispanic 1 = black, non-Hispanic
HISP	Dichotomous variable to indicate Hispanic ethnicity	0 = non=Hispanic 1 = Hispanic
OTHER	Dichotomous variable to indicate race/ethnicity other than non-Hispanic black, non-Hispanic white or Hispanic. Includes Asian, Native American, mixed and unknown race	0 = black, white or Hispanic 1 = not black, white or Hispanic
Y1	Indicator for 20 weeks gestation in 2001	0 = Not 20 weeks gestation in year 2001 1 = 20 weeks gestation in year 2001
Y2	Indicator for 20 weeks gestation in 2002	0 = Not 20 weeks gestation in year 2002 1 = 20 weeks gestation in year 2002
Y3	Indicator for 20 weeks gestation in 2003	0 = Not 20 weeks gestation in year 2003 1 = 20 weeks gestation in year 2003
Y4	Indicator for 20 weeks gestation in 2004	0 = Not 20 weeks gestation in year 2004 1 = 20 weeks gestation in year 2004
Y5	Indicator for 20 weeks gestation in 2005	0 = Not 20 weeks gestation in year 2005 1 = 20 weeks gestation in year 2005

Results

Exposure data. Ambient air pollution emission exposure from 977 TRI sites was estimated for 21,314 births. Prevalence of exposure varied by exposure group from 1.14 percent exposed (PACs) to 13.54 percent exposed (total emissions). Table 6 shows descriptive statistics for each exposure of interest (exposed vs. unexposed) and respective level of exposure (low, medium or high exposure vs. no exposure).

Outcome data. Preterm birth comprised 8.53% of total births, and low birth weight comprised 5.82% of total births. Non-Hispanic blacks had a higher prevalence of preterm birth (11.31%) than both non-Hispanic whites (7.61%) and Hispanics (8.76%). Non-Hispanic blacks also had a higher prevalence of low birth weight (9.58%) than both non-Hispanic whites (4.86%) and Hispanics (5.62%).

Younger gestational age was associated with lower birth weight, less maternal education, tobacco use during pregnancy, later or no prenatal care, breech presentation, caesarean birth, black infants and male infants. Lower birth weight was associated with younger gestational age at birth, less maternal education, tobacco use during pregnancy, later or no prenatal care, breech presentation, caesarean birth, black infants, female infants and no previous births.

Population characteristics. Mothers in the study population were predominantly non-smoking (94.73%), Hispanic (48.55%), and married (65.59%), with highest education level of 12^{th} grade or less (61.10%). On average, mothers exposed to any point source air emissions were much more likely to be married (60.24% vs. 33.48%) and Hispanic (60.96% vs. 46.61%) and less likely to have completed 12^{th} grade (25.55% vs. 39.65%) than mothers not exposed to any point source air emissions. Table 7 provides detailed descriptive statistics of the study population.

Estimates of effect. The adjusted logistic models show a slight increase in the odds of preterm birth for subjects exposed to any point source air emissions (OR = 1.040), the ten TRI-CHIP chemicals (OR = 1.088), PACs (OR = 1.147) and benzene (OR = 1.053) but none were significant at the α=0.05 level. There is no evidence of a dose-response relationship from the zero, low, medium and high levels of exposure for any exposure group, possibly due to inadequate sample sizes. Table 8 shows the odds ratios and 95% confidence intervals for preterm birth and all exposures of interest by level of exposure.

The adjusted logistic models show no positive association between low birth weight and any exposure groups. Table 9 shows the odds ratios and 95% confidence intervals for low birth weight and all exposures of interest by level of exposure.

Race/ethnicity. There was no consistent overall pattern in the difference in odds of preterm delivery between racial/ethnic groups. There was a moderately increased odds ratio for non-Hispanic blacks (OR=1.213) exposed to TRI-CHIP 10 chemicals compared to non-Hispanic whites (OR=1.150) and Hispanics (OR=1.037). There was a largely increased odds ratio for Hispanics (OR=1.379) compared to non-Hispanic blacks (OR=0.811) and non-Hispanic whites (OR=0.776). However, no odds ratios were significant at the α=0.05 level. Table 10 shows the odds ratios and 95% confidence intervals for preterm birth and all exposures of interest by race/ethnicity.

Results for odds of low birth weight were generally null or slightly protective across all race/ethnicity categories. However, the odds ratios in the benzene exposure group were largely increased for both non-Hispanic whites (OR=1.1423) and non-Hispanic blacks (OR=1.312) compared to Hispanics (OR=0.509). There was also a moderately increased odds ratio for non-Hispanic blacks (OR=1.281) for the TRI-CHIP

10 exposure compared to non-Hispanic whites (OR=0.747) and Hispanics (OR=0.950). No odds ratios were significant at the α=0.05 level. Table 11 shows the odds ratios and the 95% confidence intervals for low birth weight and all exposures of interest by race/ethnicity.

2005 sub-analysis. There was no clear overall pattern of difference in odds of preterm delivery or LBW between the total study population and the 2005 sub-population, and no differences in odds were statistically significant for any exposure group. However, in the benzene exposure group, the 2005 sub-population did have a moderately elevated odds of PTB (OR=1.422) and a largely elevated in odds of LBW (OR=2.167) compared to the total study population (PTB OR=1.053, LBW OR=0.826).

After adjusting the 2005 sub-population for additional variables (maternal diabetes mellitus and Medicaid delivery payment method), there were no significant differences in odds ratios for PTB or LBW for any exposure group in the expanded 2005 sub-analysis model compared with original 2005 sub-analysis model. In general, adjusting for these additional variables caused the odds ratio estimates to move slightly towards the null, with the exception of PTB in the PACs exposure group and LBW in the HAPs exposure group. Table 12 shows the odds ratios and the 95% confidence intervals for PTB, LBW, and all exposures of interest for the total population, the 2005 sub-population, and the 2005 sub-population adjusted for the additional variables.

Seasonality. The prevalence of preterm delivery in the study population peaked during late fall and winter months (October through February) with the highest prevalence in February and lowest prevalence in July. The seasonal pattern for prevalence of LBW in the study population was less evenly distributed, with the highest

prevalence in February and the lowest prevalence in September. Table 14 shows prevalence of PTB and LBW in the total study population by month.

Calendar year. Odds ratios for the no-interaction logistic models expanded to include indicator variables for year of exposure where nearly identical to the odds ratios of the original no-interaction logistic models for all exposure groups of interest for both preterm birth and low birth weight. This suggests that despite the trend of increasing prevalence of PTB and LBW over time, there was no confounding by exposure year.

Missing data. Analysis of missing data shows that missing mother's education and missing parity data had negligible influence on the estimates of effect. Replacing missing mother's education data where missing values were assumed highest or assumed lowest did not meaningfully affect the odds of PTB or LBW for any exposure group. Similarly, replacing missing parity data for where missing values were assumed parous or assumed non-parous did not meaningfully affect the odds of PTB or LBW. Table 16 shows odds ratios and 95% confidence intervals for PTB and LBW and all exposures of interest where missing mother's education data were assumed lowest, excluded or assumed highest. Table 17 shows odds ratios and 95% confidence intervals for PTB and LBW and all exposures of interest where missing parity data were assumed non-parous, excluded or assumed parous.

Table 6. Descriptive statistics of exposure variables (n = 21,188)					
Exposure	**Unexposed**	**Exposed**			
		Any	**Low**	**Medium**	**High**
Total point source air emissions	18,319 (86.46%)	2,868 (13.54%)	1031 (4.87%)	968 (4.57%)	870 (4.11%)
Hazardous Air Pollutants (HAPs)	18,686 (88.19%)	2,502 (11.81%)	859 (4.05%)	934 (4.41%)	709 (3.35%)
10 TRI-CHIP chemicals	20,055 (94.65%)	1,133 (5.35%)	327 (1.54%)	419 (1.98%)	387 (1.83%)
Metals and metal compounds	19,872 (93.79%)	1,316 (6.21%)	547 (2.58%)	437 (2.06%)	332 (1.57%)
Polyacyclic aromatic compounds (PACs)	20,946 (98.86%)	242 (1.14%)	124 (0.59%)	67 (0.32%)	51 (0.24%)
Benzene	20,929 (98.78%)	259 (1.22%)	116 (0.55%)	99 (0.47%)	44 (0.21%)

Table 7. Descriptive statistics of the study population						
	Study Population	**Exposure Status (total air emissions)**		**Race/Ethnicity**		
Variables	**N=21,314**	**Exposed N=2,892**	**Unexposed N=18, 422**	**White, NH N=7,715**	**Black, NH N=2,369**	**Hispanic N=10,349**
Gestational age (weeks)	38.58 ± 2.00					
Term birth (%) (≥37 weeks)	90.88	90.11	91.00	91.92	87.93	90.58
Preterm birth (%) (<37 weeks)	8.53	9.09	8.44	7.61	11.31	8.76
Very preterm birth (%) (<32 weeks)	1.25	1.45	1.21	0.80	2.24	1.32
Birth weight (grams)	3307.70 ± 548.55					
Normal birth weight (≥2,500g)	94.14	94.19	94.14	95.10	90.33	94.36
Low birth weight (<2,500g)	5.82	5.74	5.83	4.86	9.58	5.62
Very low birth weight (<1,500g)	0.96	1.04	0.95	0.69	90.33	0.92
Mother's age (years)	26.37 ± 6.09	25.69 ±6.09	26.48 ±6.08	27.60 ±5.99	25.09 ±6.07	25.46 ±5.96
Mother's marital status (%)						
Married	65.59	60.24	33.48	77.56	62.60	61.33
Not married	34.32	39.66	66.43	22.29	37.36	38.61
Mother's race/ethnicity (%)						
Hispanic	48.55	60.96	46.61	-	-	100.00
Non-Hispanic Black	11.11	12.00	10.98	-	100.00	-
Non-Hispanic White	36.20	23.58	38.18	100.00	-	-

Other	4.13	3.46	4.23	-	-	-
Asian	3.74	2.97	3.86	-	-	-
Native American	0.20	0.21	0.20	-	-	-
Mother's education (%)						
<12 (no diploma)	31.42	42.57	29.67	12.99	20.09	49.69
12 (diploma or GED)	29.68	30.36	29.57	28.01	40.52	29.11
13-15 (some college)	18.19	14.52	18.76%	23.77	24.36	12.74
≥16 (college grad/above)	19.55	11.03	20.89	34.47	13.68	7.20
Mother's tobacco use during pregnancy (%)						
No (0 cigarettes per day)	94.73	95.06	94.69	89.33	94.85	98.38
Yes	5.26	4.94	5.31	10.66	5.15	1.62
1-5 cigarettes per day	2.21	1.90	2.26	3.55	2.79	1.24
6-10 cigarettes per day	2.03	1.97	2.04	4.60	1.82	0.29
>10 cigarettes per day	1.03	1.07	1.02	2.51	0.55	0.10
Parity (%)						
No	38.01	39.49	38.30	41.96	37.95	34.14
Yes	58.96	60.52	58.71	55.21	59.26	59.68
1	30.47	29.32	30.65	32.53	28.62	29.39
2	17.27	17.46	17.24	15.05	17.56	19.40
≥3	11.22	13.74	10.82	7.63	13.08	10.89
Gravidity (%)						
No	33.55	32.43	33.73	35.58	31.58	31.67
Yes	65.22	66.15	65.08	63.56	67.20	66.96
Mode of delivery (%)						
Vaginal/spontaneous	67.36	69.92	66.99	66.38	66.10	68.79
Vaginal/forceps	1.46	1.31	1.48	1.85	1.18	1.17
Vaginal/vacuum	2.85	2.56	2.88	3.16	2.15	2.56
Caesarean	28.21	26.18	28.50	28.45	30.39	27.41
Fetal Presentation (%)						
Breech	2.54	2.32	2.58	2.90	1.82	2.37
Cephalic	97.46	97.68	97.42	97.10	98.18	97.63
Month prenatal care began (%)						
1^{st}-3^{rd} month	77.75	73.35	78.45	85.56	74.84	72.05
4^{th}-6^{th} month	15.07	18.46	14.53	9.96	16.97	18.84
7^{th}-9^{th} month	3.05	3.39	3.00	2.24	3.59	3.61
No prenatal care	4.13	4.81	4.02	2.24	4.60	5.50
Child's sex (%)						
Male	50.73	50.45	50.92	49.42	49.89	49.12
Female	49.27	49.55	49.08	50.58	50.11	50.88
Medicaid (% 2005 data)						
No	57.30	54.07	59.56	66.11	38.96	53.83
Yes	40.06	45.93	40.44	32.55	59.44	42.79
Diabetes (% 2005 data)						
No	96.56	96.48	96.53	96.86	96.79	96.43
Yes	3.21	3.52	3.43	3.14	3.21	3.56
Gestational	0.41	0.70	0.37	0.40	0.20	0.41
Pre-pregnancy	3.03	2.82	3.06	2.74	3.01	3.16

Year of birth (%)						
2001	18.07	18.78	17.96	18.91	17.64	17.55
2002	20.64	20.33	20.69	20.51	20.98	20.68
2003	19.79	20.47	19.68	20.12	19.25	19.69
2004	20.92	20.78	20.94	21.08	21.11	20.65
2005	20.58	19.64	20.73	19.39	21.02	21.43
Month of birth (%)						
January	8.33	9.44	8.15	8.35	8.70	8.17
February	7.44	6.43	7.60	7.82	7.22	7.20
March	7.86	7.75	7.88	8.20	7.34	7.60
April	7.73	7.33	7.79	7.88	7.22	7.7%
May	8.13	8.64	8.04	8.10	7.98	8.13
June	7.87	8.02	7.84	8.08	6.84	7.94
July	8.84	8.54	8.89	9.13	8.82	8.71
August	9.19	9.44	9.15	8.87	9.75	9.39
September	8.67	8.89	8.64	8.54	8.82	8.82
October	8.84	9.16	8.79	8.49	9.54	8.90
November	8.35	8.26	8.36	7.83	9.46	8.47
December	8.76	8.09	8.86	8.72	8.32	8.88

Table 8. Odds ratios for preterm birth by level of exposure					
	Crude OR	**Adjusted OR**			
Exposure level	**Any**	**Any**	**Low**	**Medium**	**High**
Total Air Emissions	1.088 (0.949, 1.248)	1.040 (0.903, 1.798)	1.014 (0.810, 1.269)	1.141 (0.914, 1.425)	0.958 (0.744, 1.232)
HAPs	1.031 (0.890, 1.195)	0.990 (0.851, 1.153)	0.964 (0.751, 1.237)	0.974 (0.767, 1.238)	1.045 (0.799, 1.366)
TRI-CHIP 10	1.167 (0.954, 1.429)	1.088 (0.883, 1.341)	**1.451 (1.027, 2.050)**	1.097 (0.784, 1.535)	0.804 (0.544, 1.188)
Metals	1.053 (0.866, 1.280)	0.980 (0.800, 1.200)	0.914 (0.667, 1.251)	1.012 (0.718, 1.426)	1.051 (0.718, 1.426)
PACs	1.287 (0.854, 1.939)	1.147 (0.754, 1.745)	1.033 (0.566, 1.884)	1.197 (0.544, 2.634)	1.382 (0.585, 3.267)
Benzene	1.244 (0.833, 1.858)	1.053 (0.688, 1.612)	1.150 (0.630, 2.102)	0.572 (0.231, 1.412)	1.953 (0.862, 4.425)

Table 9. Odds ratios for low birth weight by level of exposure					
	Crude OR	**Adjusted OR**			
Exposure level	**Any**	**Any**	**Low**	**Medium**	**High**
Total Air Emissions	0.984 (0.832, 1.165)	0.894 (0.749, 1.067)	1.039 (0.798, 1.352)	0.854 (0.644, 1.160)	0.755 (0.543, 1.049)
HAPs	0.897 (0.746, 1.078)	**0.821 (0.677, 0.996)**	0.981 (0.732, 1.315)	0.760 (0.555, 1.041)	0.706 (0.786, 1.025)
TRI-CHIP 10	1.048 (0.816, 1.346)	0.971 (0.748, 1.259)	1.064 (0.671, 1.686)	1.030 (0.682, 1.556)	0.837 (0.529, 1.322)
Metals	1.041 (0.824, 1.316)	0.956 (0.748, 1.221)	0.887 (0.606, .1.300)	1.038 (0.693, 1.555)	0.965 (0.602, 1.545)
PACs	1.057 (0.625, 1.788)	0.899 (0.520, 1.554)	0.982 (0.476, 2.204)	0.731 (0.228, 2.342)	0.907 (0.279, 2.945)
Benzene	0.987 (0.584, 1.667)	0.826 (0.470, 1.453)	0.672 (0.273, 1.654)	0.536 (0.169, 1.700)	1.886 (0.730, 4.868)

Table 10. Adjusted odds ratios for preterm birth by race/ethnicity				
	Overall	**Black, NH**	**White, NH**	**Hispanic**
Total Air Emissions	1.040 (0.903, 1.798)	1.085 (0.487, 1.227)	1.077 (0.816, 1.421)	1.096 (0.928, 1.331)
HAPs	0.990 (0.851, 1.153)	0.801 (0.532, 1.204)	0.940 (0.689, 1.282)	1.065 (0.878, 1.291)
TRI-CHIP 10	1.088 (0.883, 1.341)	1.213 (0.733, 2.009)	1.150 (0.735, 1.799)	1.037 (0.793, 1.355)
Metals	0.980 (0.800, 1.200)	0.649 (0.362, 1.164)	1.161 (0.779, 1.729)	1.006 (0.778, 1.301)
PACs	1.147 (0.754, 1.745)	0.811 (0.285, 2.305)	0.776 (0.239, 2.523)	1.379 (0.837, 2.269)
Benzene	1.053 (0.688, 1.612)	0.772 (0.232, 2.564)	1.151 (0.456, 2.906)	1.096 (0.651, 1.847)

Table 11. Adjusted odds ratios for low birth weight by race/ethnicity				
	Overall	**Black, NH**	**White, NH**	**Hispanic**
Total Air Emissions	0.894 (0.749, 1.067)	0.684 (0.439, 1.066)	0.857 (0.597, 1.229)	0.985 (0.784, 1.238)
HAPs	0.821 (0.677, 0.996)	0.750 (0.477, 1.179)	0.679 (0.445, 1.036)	0.909 (0.709, 1.165)
TRI-CHIP 10	0.971 (0.748, 1.259)	1.281 (0.753, 2.177)	0.747 (0.393, 1.422)	0.950 (0.676, 1.335)
Metals	0.956 (0.748, 1.221)	0.796 (0.442, 1.432)	0.840 (0.486, 1.453)	1.057 (0.776, 1.441)
PACs	0.899 (0.520, 1.554)	1.012 (0.355, 2.888)	1.146 (0.351, 3.750)	0.780 (0.363, 1.675)
Benzene	0.826 (0.470, 1.453)	1.312 (0.453, 3.802)	1.423 (0.508, 3.985)	0.509 (0.208, 1.247)

Table 12: 2005 data ORs						
	Preterm birth			Low birth weight		
	All births	2005 births only	2005 births adjusted for Medicaid, diabetes	All births	2005 births only	2005 births adjusted for Medicaid, diabetes
Total Air Emissions	1.040 (0.903, 1.798)	1.008 (0.618, 1.646)	0.995 (0.609, 1.627)	0.894 (0.749, 1.067)	1.070 (0.599, 1.913)	1.058 (0.591, 1.894)
HAPs	0.990 (0.851, 1.153)	1.094 (0.648, 1.849)	1.072 (0.633, 1.815)	0.821 (0.677, 0.996)	0.928 (0.480, 1.796)	0.912 (0.470, 1.768)
TRI-CHIP 10	1.088 (0.883, 1.341)	0.773 (0.329, 1.819)	0.793 (0.337, 1.868)	0.971 (0.748, 1.259)	0.728 (0.257, 2.058)	0.751 (0.265, 2.128)
Metals	0.980 (0.800, 1.200)	0.502 (0.215, 1.169)	0.508 (0.218, 1.184)	0.956 (0.748, 1.221)	0.921 (0.411, 2.065)	0.959 (0.427, 2.157)
PACs	1.147 (0.754, 1.745)	1.283 (0.377, 4.369)	1.306 (0.383, 4.451)	0.899 (0.520, 1.554)	0.545 (0.072, 4.149)	0.553 (0.072, 4.218)
Benzene	1.053 (0.688, 1.612)	1.422 (0.419, 4.822)	1.420 (0.418, 4.821)	0.826 (0.470, 1.453)	2.167 (0.627, 7.493)	2.076 (0.597, 7.224)

Table 13: Annual variation in prevalence of preterm delivery and low birth weight infants					
	2001	2002	2003	2004	2005
Preterm (%)	7.76	7.98	8.37	9.33	9.10
LBW (%)	5.37	5.20	6.14	6.41	5.91

Table 14: Seasonal variation in prevalence of preterm delivery and low birth weight infants by month												
	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Preterm (%)	9.18	9.65	8.36	8.32	8.08	7.99	7.69	8.22	8.17	9.55	8.88	8.36
LBW (%)	5.69	6.87	6.09	6.25	5.37	6.08	5.41	5.97	5.14	5.57	6.01	5.57

Table 15: Adjusted odds ratios (AOR) for original models and expanded models with indicator variables for exposure year added				
Model	**Preterm birth AORs**		**Low birth weight AORs**	
	original	**year-expanded**	**original**	**year-expanded**
Total Air Emissions	1.040 (0.903, 1.798)	1.038 (0.901, 1.196)	0.894 (0.749, 1.067)	0.893 (0.748, 1.066)
HAPs	0.990 (0.851, 1.153)	0.989 (0.850, 1.152)	0.821 (0.677, 0.996)	0.820 (0.676, 0.994)
TRI-CHIP 10	1.088 (0.883, 1.341)	1.089 (0.883, 1.342)	0.971 (0.748, 1.259)	0.971 (0.748, 1.260)
Metals	0.980 (0.800, 1.200)	0.977 (0.797, 1.197)	0.956 (0.748, 1.221)	0.952 (0.745, 1.217)
PACs	1.147 (0.754, 1.745)	1.154 (0.758, 1.756)	0.899 (0.520, 1.554)	0.907 (0.525, 1.567)
Benzene	1.053 (0.688, 1.612)	1.053 (0.688, 1.612)	0.826 (0.470, 1.453)	0.827 (0.470, 1.454)

Table 16: Missing mother's education data						
	Preterm birth			Low birth weight		
	Missing assumed lowest	Missing data excluded	Missing assumed highest	Missing assumed lowest	Missing data excluded	Missing assumed highest
Total Air Emissions	1.043 (0.907, 1.200)	1.040 (0.903, 1.798)	1.045 (0.908, 1.202)	0.917 (0.771, 1.091)	0.894 (0.749, 1.067)	0.922 (0.775, 1.097)
HAPs	0.998 (0.858, 1.160)	0.990 (0.851, 1.153)	0.999 (0.860, 1.161)	0.843 (0.697, 1.018)	0.821 (0.677, 0.996)	0.848 (0.702, 1.024)
TRI-CHIP 10	1.105 (0.899, 1.359)	1.088 (0.883, 1.341)	1.107 (0.900, 1.361)	0.998 (0.774, 1.289)	0.971 (0.748, 1.259)	1.004 (0.778, 1.295)
Metals	0.990 (0.810, 1.209)	0.980 (0.800, 1.200)	0.992 (0.812, 1.212)	0.973 (0.765, 1.238)	0.956 (0.748, 1.221)	0.980 (0.770, 1.246)
PACs	1.140 (0.749, 1.735)	1.147 (0.754, 1.745)	1.141 (0.750, 1.735)	0.890 (0.515, 1.538)	0.899 (0.520, 1.554)	0.892 (0.516, 1.541)
Benzene	1.084 (0.714, 1.646)	1.053 (0.688, 1.612)	1.086 (0.715, 1.659)	0.878 (0.509, 1.515)	0.826 (0.470, 1.453)	0.882 (0.511, 1.522)

Table 17: Missing parity data						
	Preterm birth			Low birth weight		
	Missing assumed non-parous	Missing data excluded	Missing assumed parous	Missing assumed non-parous	Missing data excluded	Missing assumed parous
Total Air Emissions	1.010 (0.888, 1.149)	1.040 (0.903, 1.798)	1.010 (0.888, 1.149)	0.875 (0.750, 1.021)	0.894 (0.749, 1.067)	0.875 (0.750, 1.021)
HAPs	0.965 (0.841, 1.108)	0.990 (0.851, 1.153)	0.966 (0.841, 1.109)	0.810 (0.685, 0.958)	0.821 (0.677, 0.996)	0.812 (0.686, 0.960)
TRI-CHIP 10	0.996 (0.819, 1.212)	1.088 (0.883, 1.341)	0.996 (0.819, 1.211)	0.850 (0.669, 1.079)	0.971 (0.748, 1.259)	0.851 (0.671, 1.081)
Metals	0.971 (0.807, 1.168)	0.980 (0.800, 1.200)	0.970 (0.807, 1.167)	0.901 (0.725, 1.120)	0.956 (0.748, 1.221)	0.902 (0.725, .121)
PACs	1.090 (0.736, 1.613)	1.147 (0.754, 1.745)	1.092 (0.737, 1.616)	0.826 (0.502, 1.360)	0.899 (0.520, 1.554)	0.826 (0.502, 1.360)
Benzene	1.079 (0.735, 1.585)	1.053 (0.688, 1.612)	1.081 (0.736, 1.588)	0.810 (0.493, 1.331)	0.826 (0.470, 1.453)	0.812 (0.494, 1.335)

Discussion

The primary objective of this study was to examine the effect of maternal residential proximity to Toxics Release Inventory (TRI) sites on gestational age at birth and birth weight. The research hypothesis that maternal residential proximity to Toxics Release Inventory (TRI) sites is associated with preterm birth and low birth weight was not supported by this analysis. However, several potential biases in the study may have concealed any true associations between TRI site-associated ambient air pollution exposure and PTB or LBW.

There was also no clear pattern of effect modification by race/ethnicity in our study population. However, small numbers of non-Hispanic blacks in the study population limited our power to detect effect modification among African American mothers. Furthermore, the 'Hispanic Birth Paradox' may have influenced our results as a large number of study participants were Hispanic. Migrant status for these individuals was unknown, so it was not possible to evaluate the extent of this potential effect.

Exposed subjects were much more likely than unexposed subjects to be married and less likely to be non-Hispanic black or African American. Both these population characteristics of the exposed group are protective against PTB and LBW. This lack of comparability between the exposed and unexposed subjects in the study population may partially explain the generally null results despite controlling for these variables in the regression models.

Strengths

A strength of this study was the relatively large sample size, with thousands of births spanning over five years. The research was focused on a geographic population with elevated risk of the outcomes of interest; study participants were from Texas, a state

in which the prevalence of PTB and LBW is consistently higher than the national average. This study also attempted to address the pervasive issue of racial/ethnic disparities in adverse birth outcomes in the analysis.

Data on several known risk factors for PTB and LBW were available and controlled for in this study, including maternal age, maternal education, parity, first-trimester prenatal care, tobacco use during pregnancy, male infant sex, marital status and race/ethnicity. The association between these risk factors and the outcomes of interest were not assumed to be linear without investigation of the data and previous literature. For example, the non-linear relationship between maternal age and the outcomes of interest were incorporated in the analyses.

There were very little missing data for any covariates, and the effect of missing data on the measures of effect were negligible. The extent to which missing data affected results was thoroughly assessed by re-assigning the missing data as one and then the other dichotomous value.

This study classified type of ambient pollutant exposure by chemical or group of chemical. In contrast to previous research studies, this refinement of exposure definition doesn't make the assumption that all ambient pollutants pose an equal risk of PTB and LBW, or that all chemicals exposures that result in adverse birth outcomes follow the same physiologic mechanism. Dose-responses relationships were also explored for all exposures of interest.

Weaknesses

Indirect exposure measurement and potential exposure misclassification were the major weaknesses in this study. Assuming that exposure misclassification was non-differential, results would be expected to be biased towards the null.

Population-level exposure does not always accurately predict individual-level exposure. Using GIS and residential proximity to assign exposure classification is less ideal than more direct measures of exposure such as biologic samples (maternal blood or fetal cord blood) or individual pollution monitors. Unfortunately, such measures of exposure are not feasible given that this was a retrospective secondary data analysis. However, the use of GIS to approximate exposure has been frequently used in previous environmental epidemiology research.

The decision to use a one-mile radius to determine exposure status was based on maintaining consistency with previous research but did not consider factors that would influence the distance or direction of travel of ambient chemicals. An exposure radius that takes into account topographical and meteorological features of the environment would more accurately estimate exposure status. Additionally, variation in the chemical properties of the exposure groups of interest may result in differences in appropriate radius of exposure. This was beyond the scope of this study.

Residential address can be useful proxy for assessing maternal ambient air pollution exposure because pregnant women generally spend the majority of their time at or near their home[66]. However, it is important to examine residential mobility and patterns of mobility during pregnancy to estimate the extent of exposure misclassification and bias of associations. Previous literature has estimated residential mobility during pregnancy ranges between 12-31%[67-72] with mobility estimates the highest in a Texas

population[72]. Residential address during the critical window of exposure was unavailable, so we used the address at time of conception. The extent of maternal residential mobility within the study population is unknown and may be a significant source of bias within the study.

Data for diabetes and socioeconomic status (Medicaid payment) were only available for births in 2005. There was no significant difference in the 2005 sub-analysis in which models were expanded to include these data in comparison to the models without these data. However, lack of data for these known risk factors of PTB and LBW may have nonetheless affected study results.

Additional covariates that could potentially confound results include exposure to intimate partner violence, alcohol consumption during pregnancy, maternal pre-pregnancy BMI and weight gain during pregnancy. These data might also provide additional insight into potential effect modification by race/ethnicity.

Conclusion

This study found no evidence of a relationship between maternal residential proximity to TRI sites and preterm birth for any chemical exposure groups of interest. Similarly, there was no evidence of a relationship between maternal residential proximity to TRI sites and low birth weight for any chemical exposure groups of interest. However, the null results of this study may be partially attributable to non-differential exposure misclassification or other sources of bias.

Despite the lack of statistically significant or consistent results in this study, the body of previous research supporting the relationship between ambient air pollution exposure and adverse birth outcomes cannot be ignored. Even small associations between environmental exposures and PTB and LBW are cause for concern given the pervasiveness and severity of these adverse birth outcomes. Additional research focusing on the relationship between ambient exposure to specific chemicals or specific chemical groups with more direct measures of exposure classification than maternal residential proximity is warranted. Additionally, future environmental research is needed to explore the difference in the etiology of adverse birth outcomes between racial/ethnic groups, and especially disparities among African American mothers.

Continued and expanded requirements for environmental pollutant reporting via programs like the Toxics Release Inventory Program is recommended to increase the public's awareness of potential toxic exposures, to inform the health policy decisions of public officials and to enable future scientific investigation of potential risk factors for adverse health outcomes.

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