ASSOCIATIONS BETWEEN AMBIENT LEVELS OF COMBUSTION POLLUTANTS AND SMALL FOR GESTATIONAL AGE INFANTS IN TEXAS

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DEDICATION

To Arthur & Flora Inge and Warren & Alice Maypole

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PREFACE

This doctoral dissertation is presented as three separate manuscripts for publication. Chapter I is an introduction to the project with background information to support the hypothesis that there is an association between maternal exposure to combustion pollutants and small for gestational age infants. Chapters II, III, and IV of the dissertation were written in manuscript form suitable for publication in *Environmental Health Perspectives, Ethnicity and Disease, and Environmental Health*, respectively. Chapter V provides a synopsis of results, strengths and limitations, and recommendations for future work.

This dissertation used data from the Texas Department of State Health Services (TX DSHS), U.S. Environmental Protection Agency (EPA), and Texas Department of Transportation (TX DOT).

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There is scant evidence regarding the associations between ambient levels of combustion pollutants and small for gestational age (SGA) infants. No studies of this type have been completed in the Southern United States. The main objective of the project presented was to determine associations between combustion pollutants and SGA infants in Texas using three different exposure assessments.

Birth certificate data that contained information on maternal and infant characteristics were obtained from the Texas Department of State Health Services (TX DSHS). Exposure assessment data for the three aims came from: (1) U.S. Environmental Protection Agency (EPA) National Air Toxics Assessment (NATA), (2) U.S. EPA Air Quality System (AQS), and (3) TX Department of Transportation (DOT), respectively. Multiple logistic regression models were used to determine the associations between combustion pollutants and SGA.

For the first study looked at annual estimates of four air toxics at the census tract level in the Greater Houston Area. After controlling for maternal race, maternal education, tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census tract income level, adjusted ORs and 95% confidence intervals (CI) for exposure to PAHs (per 10 ng/m^3), naphthalene (per 10 ng/m^3), benzene (per 1 μg/m^3), and diesel engine emissions (per 10 μg/m^3) were 1.01 (0.97 – 1.05), 1.00 (0.99 – 1.01), 1.01 (0.97

– 1.05), and 1.08 (0.95 – 1.23) respectively. For the second study looking at Hispanics in El Paso County, AORs and 95% confidence intervals (CI) for increases of 5 ng/m^3 for the sum of carcinogenic PAHs (Σ c-PAHs), 1 ng/m^3 of benzo[a]pyrene, and 100 ng/m^3 in naphthalene during the third trimester of pregnancy were 1.02 (0.97 – 1.07), 1.03 (0.96 – 1.11), and 1.01 (0.97 – 1.06), respectively. For the third study using maternal proximity to major roadways as the exposure metric, there was a negative association with increasing distance from a maternal residence to the nearest major roadway (Odds Ratio (OR) = 0.96; 95% CI = 0.94 - 0.97) per 1000 m); however, once adjusted for covariates this effect was no longer significant (AOR = 0.98; 95% CI = 0.96 – 1.00). There was no association with distance weighted traffic density (DWTD).

This project is the first to look at SGA and combustion pollutants in the Southern United States with three different exposure metrics. Although there was no evidence of associations found between SGA and the air pollutants mentioned in these studies, the results contribute to the body of literature assessing maternal exposure to ambient air pollution and adverse birth outcomes.

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CHAPTER I: COMBUSTION AIR POLLUTANTS AND SMALL FOR GESTATIONAL AGE INFANTS

Specific Aims

Ambient polycyclic aromatic hydrocarbons, PAHs, are a group of chemicals that are produced by incomplete combustion of organic material in both mobile (e.g., vehicular traffic) and non-mobile (e.g., residential wood burning and coal-fired power plants) sources. Intrauterine growth restriction (IUGR) is a condition that refers to the deviation and reduction in expected fetal growth patterns. Infants born with this condition have been shown to be predisposed to adult morbidities such as hypertension, coronary heart disease, and type-II diabetes as well as neurodevelopmental disorders.[1-3] In experimental studies, DNA-PAH adducts have been found to be embryotoxic as well as fetotoxic.[4] Additionally PAHs have been found in the placenta[5-6], umbilical cord blood[7-10], and human endometrium[11] in epidemiological, experimental, and clinical studies. There is scant evidence from the epidemiological literature that PAHs are linked to IUGR[12-14]; thus, this research filled a gap in the literature regarding adverse birth outcomes associated with maternal exposure to PAHs.

The hypothesis of this research was that pregnant women exposed to higher than background levels of PAHs are more likely to have infants with IUGR. This research used two definitions of growth restriction: (1) small for gestational age (SGA), or fetal weight below the 10^{th} percentile for fetal gestational age and sex; and (2) fetal growth ratio (FGR), or birth weight of infant divided by the mean birth weight for their gestational age and sex that is less than the 85^{th} percentile. We evaluated this hypothesis in three separate

investigations: (1) in the state of Texas (TX), (2) El Paso County, TX, and (3) Harris County, TX. Each study used a different measure of exposure to ambient air pollutants, namely, modeled predicted values (TX), estimates of maternal residential PAH levels from routine monitoring data (El Paso County), and a metric based on maternal residential proximity to major roadways (Harris County). The specific aims of the study were:

- **Aim #1:** Determine the association between modeled census-tract annual estimates of four air toxics ($\sum$ c-PAHs, benzene, naphthalene, diesel engine emissions) in ambient air, obtained from the 2002 U.S. Environmental Protection Agency (EPA) National Air Toxics Assessment (NATA), and SGA among infants born in 2002 in the Greater Houston Area.

- **Aim #2:** Examine the critical window of exposure to PAH levels during pregnancy on SGA using ambient air monitoring data collected in El Paso County, Texas, 2005-2007.

- **Aim #3:** Assess the association between maternal residential proximity to traffic and SGA in Harris County, Texas, 2006.

This research evaluated the magnitude of the effects of PAHs in ambient air on IUGR and identified sub-populations of pregnant women who may be at greater risk for this adverse birth outcome due to air pollution. Since PAHs may be adsorbed onto particulate matter, this research had the potential to provide additional scientific evidence to support the current

annual U.S. Environmental Protection Agency's National Ambient Air Quality Standard (NAAQS) for fine particulate matter ($PM_{2.5}$).[15]

Background and Significance

Intrauterine Growth Restriction

Intrauterine Growth Restriction (IUGR) Definition: IUGR is a condition that refers to the deviation in the rate of fetal growth as to the expected rate of fetal growth. It is estimated that the incidence of IUGR is approximately five percent of the general obstetric population;[16] however, this could vary with the population under study. A reduction in fetal growth may lead to fatality in newborns.[17-19] Additionally, studies have linked IUGR to adult morbidities such as type-II diabetes, hypertension, and coronary heart disease.[1-3]

Two Types of IUGR: There are two types of IUGR: symmetric and asymmetric. Symmetric IUGR comprises 20-30% of those infants born growth restricted while asymmetric IUGR comprises the remaining 70-80%.[17-18] Symmetric IUGR refers to a fetus whose growth restriction is proportional across the fetus. Symmetric IUGR occurs early in pregnancy due to an insult such as a chemical exposure, viral infection, or developmental abnormalities.[19] Asymmetric growth restriction occurs when the fetus directs energy to maintaining growth to vital organs at the expense of the liver, muscle, and fat. A fetus with asymmetric IUGR will have a normal head dimension but a small abdominal circumference, thin limbs, and decreased subcutaneous tissue.[20]

Medical Factors affecting Fetal Growth Restriction: Fetal growth restriction is controlled by three main factors: fetal, placental, and maternal (See Table 1 adapted from Peleg et al.[20], Oelberg[17], Lin and Santolaya-Forgas[18], and Monk and Moore[19]). Among the

fetal factors, chromosomal abnormalities such as trisomy 13, 18, and 21, monosomy (i.e., 45 XO), deletions, uniparental disomy, and placental mosaicism restrict fetal growth. Congenital malformations (e.g., anencephaly or diaphragmatic hernia) also restrict fetal growth as do multiple gestations. Placental factors include abnormal trophoblastic invasion and multiple placental infarctions. Lastly, examples of maternal factors that contribute to fetal growth restriction include but are not limited to severe lung disease (hypoxic effects), chronic hypertension (vascular complications), and glomerulonephritis (renal complications).[18]

Table 1. Medical Risk Factors Associated with Intrauterine Growth Restriction

Fetal Factors	Placental Factors	Maternal Factors
Chromosomal abnormalities	Abnormal Trophoblastic Invasion	Genetic/Constitutional
Congenital Malformations	Multiple Placental Infarctions	Nutrition
Multiple Gestations	Umbilical-Placental Vascular Anomalies	Hypoxic Effects
	Abnormal Cord Insertion	Vascular Complications
	Placenta Previa	Renal Complications
	Circumvallated Placenta	Antiphosholipid Antibodies
	Chorioangiomata	Environment and Drugs
		Poor Obstetric History

Diagnosis and Management of IUGR: Diagnosis of IUGR during pregnancy is most often achieved through serial ultrasound examinations. Measurements used are the biparietal diameter, head circumference, abdominal circumference, and femur length. Each measurement has an associated percentile and a fetal weight can then be calculated. Additionally important to the diagnosis of IUGR is gestational age. If gestational age is unknown, serial scans at two- to three-week intervals are typically performed to diagnosis IUGR. Another important use of ultrasound examinations is the ability to determine the amount of amniotic fluid. A decreased volume of amniotic fluid is present in most cases of

IUGR.[20] Additionally, fundal height (distance from top of the pubic symphysis to the dome of the uterine fundus) that lags by more than 3 cm or does not correspond to the expected fundal height gestational age may signal IUGR.[20] Because fetal chromosomal disorders may cause symmetric restriction, a sonogram may identify fetal abnormalities and karyotyping may determine if aneuploidy is present. Management of IUGR includes treatment of maternal factors especially maternal hypertension and diet.[20] However, in general, it is very difficult to reverse IUGR once diagnosed.

Epidemiological Risk Factors for IUGR: Medical risk factors for IUGR consist of factors found in Table 1. Additional risk factors include extremes in maternal age, less than high school level education, alcohol and cigarette use, nulliparity, and race/ethnicity other than non-Hispanic White. Other socioeconomic measures such as marital status, maternal employment, median household income, median age of houses, and median value of houses in census tracts have all been evaluated as potential confounders in previous studies of PAHs and IUGR (Appendix 1).[7-10, 12-14, 21-25]

Regarding race/ethnicity, Frisbie and colleagues found that African-American women were significantly more likely to have an infant born with IUGR as compared to non-Hispanic Whites (Anglos) in two separate models (Odds Ratio (OR) 1.4, 95% Confidence Interval (CI) 1.2-1.6; OR 1.4, CI 1.1-1.7) where the first model contained solely race/ethnicity and the second model contained sociodemographic (e.g., race/ethnicity, maternal age, maternal nativity, marital status, and parity) and socioeconomic (e.g., maternal education, and annual household income,) covariates.[26] Additionally, no difference in IUGR was reported for Mexican-American mothers as compared to Anglos in either of the two

models that were evaluated (OR = 0.9, 95 % CI = 0.7-1.2; OR = 1.0, 95 % = CI 0.7-1.3).[26] The authors suggested that socioeconomic status and demographic risk factors for IUGR in Mexican-American infants were likely present; however, the cultural components such as good nutrition and avoidance smoking and unhealthy behaviors may off-set the risk of IUGR.[26] Balcazar found a reduced odds ratio in Mexican-American infants as compared to Anglos in his study. However, upon further stratification, he found that U.S.-born Mexican-American mothers were significantly more likely to have an IUGR infant as compared to mothers born in Mexico.[27] In Texas, where this research focused its efforts, fifty percent of births per year are Hispanic, while Black and other race/ethnicities comprise approximately fifteen percent of Texas births per year. Thus, this study made a special effort to assess the effect of combustion pollutant exposure on IUGR as modified by race/ethnicity, U.S.-born/Foreign-born mothers, and socioeconomic status.

Polycyclic Aromatic Hydrocarbons

Polycyclic Aromatic Hydrocarbons Definition: Hazardous Air Pollutants (HAPs) are pollutants that are known or suspected of causing cancer or other adverse health outcomes. Polycyclic Organic Matter (POM) is a class of pollutants of which Polycyclic Aromatic Hydrocarbons (PAHs) is a category. PAHs are a group of anthropogenic and naturally occurring chemicals that are formed during incomplete combustion. PAHs can enter the air from active volcanoes, forest fires, residential wood burning, and exhaust from vehicles. Other sources of PAHs include cigarette smoke, coal fired power plants, agricultural burning, municipal and industrial waste incineration, and hazardous waste sites.[28] Due to their

semivolatile nature, these chemicals are present in air as vapors or adsorbed to the surfaces of fine particulate matter ($PM_{2.5}$). PAHs are typically found as complex mixtures and not as single compounds. Some PAHs (Figure 1) such as benzo[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenzo[a,h]anthracene, and indeno[1,2,3-c,d]pyrene have caused tumors in laboratory animals from inhalation, ingestion, or long periods of dermal contact with these substances. Human studies have shown that individuals who are exposed by inhalation or dermal contact to PAH mixtures can develop cancer. Thus, the U.S. EPA has determined the above listed chemicals as B2 (probable) carcinogens meaning there is sufficient evidence in animal studies, but limited or no evidence in epidemiological studies.[28]

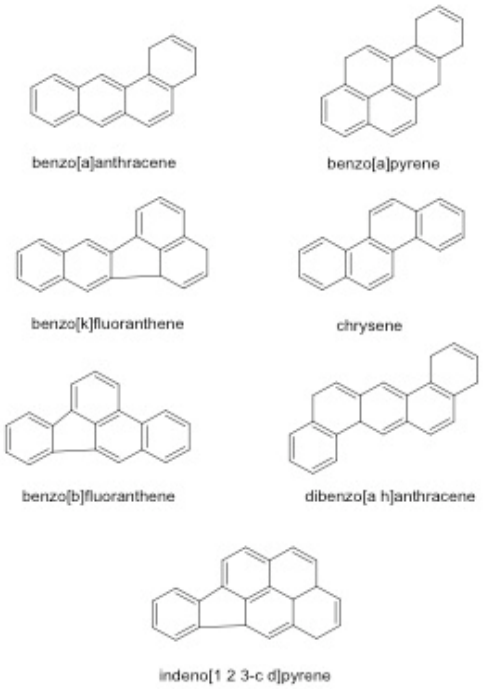

Figure 1. Carcinogenic Polycyclic Aromatic Hydrocarbon (c-PAH) Structures

PAHs and IUGR

There are limited epidemiological studies that have explored associations between PAHs and adverse birth outcomes (Appendix 1).[7-10, 12-14, 21-25] Many of the studies measured fetal growth by head circumference, length, and birth weight; however, three studies specifically used the population-based definition of IUGR, i.e., birth weight <10th percentile of gestational age and sex. The findings of these three studies are as follows. First, Dejmek and colleagues completed a retrospective cohort study in 2000 that studied the impact of c-PAHs and fine particles on IUGR in Teplice and Prachatice, Bohemia, Czech Republic.[12] There was an increased risk of IUGR after exposure to particles in the first gestational month (GM) in Teplice, but not in Prachatice due to low levels of particulate matter (PM). The adjusted odds ratio (AOR) for IUGR among fetuses exposed to medium levels of c-PAHs in the first GM was 1.60 (95% confidence interval (CI), 1.06-2.15), and among those exposed to high levels the AOR was 2.15 (95% CI, 1.27-3.63). When looking at the continuous data of c-PAH levels in Teplice, it was found that for every 10 ng increase in c-PAHs in the first GM, the AOR was 1.22 (95% CI, 1.07-1.39). A similar relationship was found in Prachatice; however, the AOR was not significant.[12]

Another group of epidemiologists evaluated the association of polycyclic organic matter (POM) with small for gestational age (SGA) in a cross-sectional study conducted in New Jersey.[13] POMs are a broad class of compounds that includes PAHs. Two separate models were evaluated that adjusted for either individual (e.g., maternal race, maternal age, infant sex, maternal education, previous pregnancy terminations, month prenatal care began,

maternal smoking, and maternal use of alcohol) or group-level (e.g., median household income, urban residence, median age of houses, median value of homes) variables. In the model that included individual-level risk factors, the adjusted odds ratio (AOR) was 1.22 (95% CI, 1.17-1.27) for mothers living in the highest exposure tertile relative to those in the lowest tertile. For the model adjusted for group-level covariates, the AOR for mothers living in the highest exposure tertile relative to those living in the lowest tertile was 1.13(95% CI, 1.07-1.18).[13]

Lastly, Choi and colleagues completed a retrospective cohort study of African-American and Dominican mother-newborn pairs from New York City.[25] Choi and colleagues defined symmetric growth restriction as an infant who was both SGA and had a fetal growth ratio (FGR) of less than 85%. It was determined that a 1 natural-log (ln) increase in prenatal PAH exposure was associated with a 2-fold increase in the risk of symmetric IUGR among full-term African-Americans pregnancies ($p<0.05$). There was a lack of association among Dominicans although their mean exposure for PAHs was similar to that of African Americans. The authors attribute reduced risk in Dominicans to healthier diets and a strong social support network.[25]

Other Pollutants and IUGR

Regarding specific air pollutants, nitrogen oxides (NO_x), carbon monoxide (CO), volatile organic compounds (VOCs), and PM have been shown to be associated with adverse birth outcomes such as low birth weight, reduced head circumference and body length[29-34] and can originate from a common source, traffic emissions. In Brisbane, Australia, Hansen

et al. found no associations between ambient PM_{10}, ozone(O_3), and nitrogen dioxide (NO_2) and IUGR (<10^{th} percentile for gestational age and gender).[35] Bobak also found in his Czech Republic study that IUGR (<10^{th} percentile of birth weight for gestational age and sex) was not associated with ambient sulfur dioxide (SO_2) (OR=0.91, 95% CI= 0.80-1.04) or total suspended particulates (TSP) (OR=0.89, 95% CI= 0.75-1.06) for a 50 $\mu g/m^3$ increase for either pollutant in the first trimester.[36] Mannes and colleagues found that ambient levels of PM_{10} ($\mu g/m^3$), $PM_{2.5}$ ($\mu g/m^3$), and O_3 (ppm) in the second trimester of pregnancy had a small but statistically significant effect on SGA (greater than two standard deviations below the mean birth weight according to gestational age) for infants born in Sydney, Australia (OR=1.01, 95% CI=1.00-1.04; OR=1.03, 95% CI=1.01-1.05; OR=1.01, 95% CI=1.00-1.01, per unit increase in pollutant concentration, respectively).[37] Most recently Liu et al. found that ambient SO_2 (OR=1.07, 95% CI 1.01-1.13, per 5 ppb increase), NO_2 (OR=1.05, 95% CI=1.01-1.10, per 10 ppb increase), and CO (OR=1.06, 95% CI=1.01-1.10, per 1 ppm increase) was associated with IUGR (<10^{th} percentile for gestational age and sex) for the first month of pregnancy.[38]

Potential Mechanisms for PAHs on IUGR

The actual mechanism by which PAHs influence fetal growth restriction in humans is not known; however, theories have been proposed. The first mechanism is oxidative stress during early stages of embryonic growth. PAHs adsorbed onto PM may lead to DNA adducts once introduced into the human body. These DNA adducts can induce biotransformation of detoxification enzymes such as cytochrome P450, epoxide hydrolase,

and dihydrodiol dehydrogenase.[39] The second mechanism by which PAHs adsorbed on PM may cause IUGR is through pulmonary and placental inflammation.[39] Guyda found that PAHs, especially benzo(a)pyrene, affect receptors of epidermal growth factor (EGF) and insulin-like growth factors (IGF) I and II of the placenta.[40] Altering these growth factors through the combination of the two mechanisms, oxidative stress and inflammation, may result in decreased fetal-placental exchange of oxygen and nutrients. The result of this may lead to impaired fetal growth.

Innovation

The proposed research was innovative because 1) the relationship between traffic-related ambient air pollution and intrauterine growth restriction has not been studied thoroughly; 2) evidence provided by this research, specifically Aim #2, helped elucidate the relationship between growth restriction and the critical exposure window of exposure for PAHs; and 3) this research took place in the Southwest United States. Most studies regarding PAHs and other combustion pollutants and adverse birth outcomes were completed in Europe[12], Asia[8], and in the Northeastern United States.[13-14, 22]

We evaluated the combustion pollutant-IUGR association using three different study designs: a cross-sectional study, a cohort study, and a case-control study. We also used different exposure metrics in each study (modeled predicted values, estimated levels from air monitoring data, and a metric based on the residential proximity of mothers to major roadways, respectively), each of which offers unique advantages in the assessment of the association between ambient combustion pollutant exposure and IUGR. Moreover, we used

two definitions to classify IUGR infants: (1) the population-based SGA definition where those infants whose fetal weight is below the 10th percentile for fetal gestational age and sex, and (2) fetal growth ratio (FGR) defined as less than the 85th percentile for birth weight divided by the mean birth weight for a given gestational age and sex. The FGR definition is used in clinical diagnoses, management, and epidemiologic investigations of the underlying etiologies of IUGR.[26] There is only one recently reported study in the air pollution-growth restriction literature that used multiple measures of intrauterine growth restriction in classifying their outcome.[14] By varying the methodological approaches in which we examined our hypothesis, we were able to more fully explore the possible combustion pollutant-IUGR association.

CHAPTER II: IMPACT OF EXPOSURE TO AMBIENT AIR TOXICS ON FETAL GROWTH AMONG NEWBORN INFANTS IN THE GREATER HOUSTON AREA

Abstract

Background There is limited epidemiological evidence regarding the associations of air toxics and adverse reproductive outcomes such as small for gestational age (SGA) infants. The Greater Houston Area has many airborne contaminants from point and mobile sources of combustion. Existing epidemiological evidence indicates that a developing fetus may be susceptible to these air toxics.

Objectives This study assessed the association between modeled census tract annual concentration estimates of four air toxics in ambient air and SGA among infants born in 2002 in the Greater Houston Area.

Methods Annual estimates of mean ambient air levels for polycyclic aromatic hydrocarbons (PAHs), benzene, diesel engine emissions and naphthalene were obtained from the 2002 U.S. Environmental Protection Agency (EPA) National Air Toxics Assessment (NATA) for Greater Houston Area census tracts. Birth records for infants born in 2002 were obtained from the Texas Department of State Health Services (TX DSHS) for the Greater Houston Area. Associations between SGA and air toxics were evaluated using logistic regression analyses.

Results After controlling for maternal race, maternal education, tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census tract income level, adjusted ORs and 95% confidence intervals (CI) for exposure to PAHs (per 10 ng/m^3), naphthalene (per 10 ng/m^3), benzene (per 1 $\mu g/m^3$), and diesel engine emissions (per 10 $\mu g/m^3$) were 1.01 (0.97 – 1.05), 1.00 (0.99 – 1.01), 1.01 (0.97 – 1.05), and 1.08 (0.95 – 1.23) respectively.

Conclusions These findings do not provide evidence of an association between annual ambient concentrations of PAHs, naphthalene, benzene or diesel engine emissions and SGA in the Greater Houston Area.

Keywords

Air pollution, Small for Gestational Age, Polycyclic Aromatic Hydrocarbons, Benzene, Diesel Engine Emissions, Naphthalene, Pregnant Woman, Prenatal Development, Child health

Introduction

The 2002 National Air Toxics Assessment (NATA) modeled 180 of the 187 Clean Air Act air Hazardous Air Pollutants (HAPS), also referred to as air toxics, as well as diesel engine emissions, which has recently been designated as a HAP, at the census tract level. The Greater Houston Area, also known as the Houston-Sugarland-Baytown Metropolitan Statistical Area, is ranked in the top ten largest metropolitan statistical areas in the United States (U.S. Census Bureau 2012a). It includes Harris, Austin, Brazoria, Chambers, Fort Bend, Galveston, Liberty, Montgomery, San Jacinto, and Waller Counties. Polycyclic aromatic hydrocarbons (PAHs), naphthalene, benzene, and diesel engine emissions are four air toxics found in the ambient air of the Greater Houston Area. Within the Greater Houston Area, major industrial sources of air toxics are seaports (Port of Houston, Texas City, and Galveston) as well as a petrochemical complex that borders the Houston Ship Channel. Vehicle exhaust also contributes to ambient air toxics due to the nearly five million area residents commuting throughout the area in 2000 (U.S. Census Bureau 2012a). It is important to study air toxics because some of these pollutants, listed above, are known or suspected to cause cancer and may cause other adverse health outcomes, e.g. adverse birth outcomes.

There are few epidemiological studies that have reported associations between ambient air pollution, and even fewer with air toxics, and an adverse birth outcome called small for gestational age (SGA). A small for gestational age (SGA) infant is one who is smaller than those of the same gestational age and sex. These are infants with a birth weight less than the tenth percentile for a given gestational age and sex (Glinianaia et al. 2004;

Woodruff et al. 2009). Intrauterine growth restriction (IUGR) refers to the deviation and reduction in expected fetal growth pattern. The fetal, placental, and maternal risk factors for growth restriction are well known; however, the contribution from ambient air pollution is not well understood. There are few studies that have examined associations between fetal growth restriction and particulate matter (PM), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) (Bobak 2000; Dejmek et al. 2000; Hansen et al. 2007; Le et al. 2012; Mannes et al. 2005), and polycyclic aromatic hydrocarbons (PAHs) (Choi et al. 2008; Dejmek et al. 2000; Vassilev et al. 2001). There are no studies that have looked at the association between air toxics other than PAHs and PM and SGA.

Because of the limited number of studies that have focused on air toxics and SGA, the aim of the present study was to determine the association between ambient air levels of PAHs, benzene, diesel engine emissions, and naphthalene using modeled estimates obtained from the 2002 U.S. Environmental Protection Agency (EPA) National Air Toxics Assessment (NATA) and SGA among infants born in the Greater Houston Area.

Methods

Study Subjects

This study was based on records of Texas birth certificates compiled by the Texas Department of State Health Services (TX DSHS) for all live births in the Greater Houston Area in 2002. Infants with birth defects were excluded by TX DSHS because many infants with birth defects have growth restriction which is presumed to be secondary to the birth defect. The total number of infants born in the Greater Houston Area in 2002 without birth

defects was 80,625. Missing values for birth weight (n = 31, 0.01%) excluded from analyses. Additionally records for infants born with less than 37 weeks gestation (n = 6,815, 8.5%), non-singleton infants (n = 2,269, 2.9%), and those with extreme values for gestational age and birth weight (n = 478, 0.6%) were omitted. Following these exclusions, the number of full-term, singleton infants who were eligible to be included in this study was 71,032 (87.9% of Greater Houston Area cohort).

The Institutional Review Boards for Texas Department of State Health Services (TX DSHS) and the University of Texas Health Science Center at Houston approved the study.

Classification of Growth Restriction

SGA infants were identified using information available on birth certificate records. Initially, two definitions to classify growth-restricted infants were used: (1) the population-based SGA definition that includes infants whose fetal weight is below the 10^{th} percentile for fetal gestational age and sex (Glinianaia et al. 2004; Oken et al. 2003; Woodruff et al. 2009), and (2) fetal growth ratio (FGR), defined as birth weight divided by the mean birth weight for a given gestational age and sex, less than 0.85 (Choi et al. 2008). Gestational age was determined by examining either gestational age calculated from the mother's last menstrual period (LMP) or clinical gestational age estimate. The gestational age calculated from the LMP was used to determine SGA if the absolute difference between the two measures of gestational age was more than 2 weeks. Analyses used the SGA variable, the more commonly used outcome found in the epidemiological literature, because SGA and FGR were highly correlated (phi coefficient(r_Φ) = 0.91).

Exposure Assessment for Air Toxics

The 2002 U.S. EPA NATA data provide annual mean estimates of ambient levels of PAHs, benzene, diesel engine emissions, and naphthalene and other air toxics for every census tract in the nation. The NATA estimates of ambient concentrations (reported in units of $\mu g/m^3$) are generated from a dispersion model called the Assessment System for Population Exposure Nationwide (ASPEN), which accounts for meteorological conditions and uses information about emissions from mobile, point, and area sources, as well as air monitoring data when it is available (U.S. EPA 2010a). The PAHs that were used in analyses were the sum of the seven carcinogenic PAHs (Σ c-PAHs): benzo[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenzo[a,h]anthracene, and indeno[1,2,3-cd]pyrene. Unit conversions from $\mu g/m^3$ to ng/m^3 were completed for Σ c-PAHs and naphthalene. The correlation among the four air toxics (quasi-normally distributed) was assessed using Pearson's correlation analysis. Mother's residence at the time of delivery (using geocoded addresses made available by the TX DSHS) was linked to the census tract NATA estimates by geographic information systems (GIS) (ArcView; Version 9.3, Environmental Systems Research Institute, Inc., Redlands, CA).

Potential Confounders

Potential confounders available from the birth records included maternal age (continuous, years), infant sex (male, female), maternal nativity (born in the U.S., not born in the U.S.), maternal marital status (not married, married), maternal weight gain (continuous, pounds), and maternal smoking (yes, no) and alcohol use (yes, no). Birth certificate data

were also used to categorize maternal race (Non-Hispanic White, Other, Black, and Hispanic), maternal education (less than high school, high school, more than high school), parity (nulliparous, one or more), number of prenatal visits (0-7, 8-10, 11-15, more than 15), and season of infant birth as warm (April – September) and cool (October – March). In addition to the individual-level information from birth records, the 2000 U.S. Census data were used to develop census tract level variables related to socioeconomic position (SEP) including median household income (less than or equal to $30,000, $30,001 -$40,000, $40,001 - $50,000, and over $50,000), median home age (less than 20 years, 20 – 29 years, 30 – 39 years, 40 or more years), and median house value (less than or equal to $50,000, $50,001 - $75,000, $75,001 - $100,000, and more than $100,000 for the census tract (U.S. Census Bureau 2012b). Pearson contingency coefficient tests were run for the census tract level variables (household income, home age, and house value) to determine correlation between those variables. Because SEP covariates were found significantly correlated (correlation coefficients ranging from 0.55 to 0.75), we chose to adjust only for the median household income, because it is the variable most commonly used as a group-level covariate in previous studies (Currie et al. 2009; Kalkbrenner et al. 2010; Perlin et al. 1995).

Statistical Analyses

Simple logistic regression was used to estimate crude odds ratios (OR) and 95% confidence intervals (95% CI) for the association between SGA and air toxics, as well as potential individual-level covariates of interest. Air pollutant concentrations were analyzed as both continuous and categorical variables. The breakdown for each pollutant was based

on the following four categories: low (less than the 25th percentile), medium (25th - 74th percentile), high (75th - 89th percentile), and very high (greater than or equal to the 90th percentile) pollutant levels (Reynolds et al. 2003). Confounding was determined to occur if the exposure - outcome association in the adjusted analysis changed the estimate of the odds ratio by 10% or more from the crude analysis. Stratified analyses were also conducted to explore the possibility of effect-measure modification by race/ethnicity. Final models were run using hierarchical logistic regression models to determine associations between ambient levels of air toxics in Greater Houston Area census tracts and SGA (PROC GLIMMIX). All statistical analyses were performed using SAS (Version 9.3, SAS Institute, Inc., Cary, NC).

Results

Air toxic concentrations in 2002 are described in Table 1. The mean concentrations of $\sum$ c-PAHs, naphthalene, benzene and diesel engine emissions in the Greater Houston Area were 12.56 ng/m^3 (range 0.97 – 273.23 ng/m^3), 58.16 ng/m^3 (range 13.18 – 365.47 ng/m^3), 1.59 μg/m^3 (range 0.21 – 8.01 μg/m^3) and 2.33 μg/m^3 (range 0.46 – 25.32 μg/m^3), respectively. In the Pearson's correlation analyses, these air toxics were all positively correlated with each other, with correlation coefficients ranging from 0.50 – 0.77, and were used independently in logistic regression models. Figure 1 provides maps of the air toxic concentrations across census tracts in the Greater Houston Area defined by exposure categories. The highest pollutant concentrations are generally found along the Houston Ship Channel and on the east side of the Inner Loop (I-610) of Houston.

Demographic characteristics of the study population are found in Table 2. Among the 71,032 Greater Houston Area infants in this cohort, 6,514 or 9.17% were classified as SGA infants in 2002. Table 2 also shows the results of simple logistic regression models between potential covariates and SGA.

Crude and adjusted results describing the association between SGA and air toxics are shown in Table 3. Based on the results from the crude logistic regression analyses, there was an increase of 8% in the odds of SGA per 10 ng/m^3 increase in $\sum$ c-PAHs (OR = 1.08, 95% CI = 1.05 – 1.11), a 2% increase in the odds of SGA per 10 ng/m^3 increase in naphthalene (OR = 1.02, 95% CI = 1.01 – 1.03), an 8% increase in odds of SGA per 1 μg/m^3 increase in benzene (OR = 1.08, 95% CI = 1.04 - 1.13), and a 26% increase in crude odds of SGA per 10 μg/m^3 increase in diesel engine emissions (OR = 1.26, 95% CI = 1.10 – 1.44). Following adjustment for maternal race, maternal education, self-reported tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census tract income, the odds ratios were attenuated and no longer statistically significant (Adjusted Odds Ratio (AOR) = 1.01 per 10 ng/m^3 increase in $\sum$ c-PAHs, 95% CI = 0.97 – 1.05; AOR = 1.00 per 10 ng/m^3 increase in naphthalene, 95% CI = 0.99 – 1.01; AOR = 1.01 per 1 μg/m^3 increase in benzene, 95% CI = 0.97 – 1.05; AOR = 1.08 per 10 μg/m^3 increase in diesel engine emissions, 95% CI = 0.95 – 1.23). Adjusted odds ratios were similar when the data were stratified by racial/ethnic groups (Data not shown).

When modeling the air toxic concentrations as a categorical variable, the crude odds ratios for air toxics for the high exposure category vs. the referent are as follows: $\sum$ c-PAHs:

OR = 1.21, 95% CI = 1.08 – 1.36; Naphthalene: OR = 1.19, 95% CI = 1.06 – 1.34; Benzene: OR = 1.22, 95% CI = 1.09 – 1.37; Diesel Engine Emissions: OR = 1.22, 95% CI = 1.08 – 1.36. In pollutant models adjusted for maternal race, maternal education, self-reported tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census tract income, the odds of SGA are diminished and were non-significant (See Table 4).

Discussion

The present study examined the associations between ambient air concentrations of four air toxics ($\sum$ c-PAHs, naphthalene, benzene, and diesel engine emissions) and SGA of newborns in the Greater Houston Area, in 2002. This is the first study to examine four different air toxics and SGA. After controlling for maternal race, maternal education, tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census tract household income, it was found that levels of the four air toxics in this study were not associated with SGA.

Prior epidemiological studies support an association with PAHs and SGA. One study evaluated the association of polycyclic organic matter (POM) with SGA, defined as those infants whose birth weight were at or below the 10^{th} percentile among their race, sex, and gestational age, in a cross-sectional study conducted in New Jersey (Vassilev et al. 2001). POMs are a broad class of compounds that includes PAHs. The crude odds ratios for the highest categorical exposure vs. the referent in the present study were similar to Vassilev et al. highest exposure category vs. referent (OR= 1.26; 95% CI = 1.22 – 1.31) for term SGA

infants. Unlike our study in which the odds ratios diminished greatly following adjustment for confounders, Vassilev et al. reported similar magnitudes for crude and adjusted odds ratios for term SGA infants (AOR = 1.22; 95% CI = 1.16-1.27) for mothers living in the highest exposure tertile (0.611 – 2.830 $\mu g/m^3$) relative to those in the lowest tertile (0.040 – 0.268 $\mu g/m^3$) (Vassilev et al. 2001). The findings of the Vassilev et al. study indicated a stronger relationship between POM and SGA when the infant was also preterm SGA (OR = 1.51, 95% CI = 1.31 – 1.75) (Vassilev et al. 2001). This study is similar to the present study because of its use of data from the 1990 U.S. Environmental Protection Agency (EPA) Cumulative Exposure Project, a precursor to the U.S. EPA NATA data.

There is only one study that has looked at the same air toxics presented in our study with another adverse birth outcome, preterm birth. Wilhelm et al. found positive associations with all four air toxics and preterm birth (PAHs (per 59.3 ng/m^3): AOR = 1.30, 95% CI = 1.15 – 1.47; naphthalene (per 52.2 ng/m^3): AOR = 1.29, 95% CI = 1.14 – 1.45, benzene (per 0.20 ppb): AOR = 1.09, 95% CI = 1.06 – 1.13; diesel $PM_{2.5}$ (per 0.99 $\mu g/m^3$): AOR = 1.11, 95% CI = 1.07 – 1.15) (Wilhelm et al. 2011). While these associations are significant, more studies should look at preterm infants, preterm SGA infants, and term SGA infants in separate outcome categories.

Epidemiological studies looking at the association between PM and SGA are inconsistent. Additionally these studies look at the window of susceptibility of SGA to PM exposure. Results from Dejmek et al. 1999 and Dejmek et al. 2000 found significant positive associations in the first gestational month for the highest exposure category of PM_{10} and $PM_{2.5}$ vs. the referent and IUGR in the Czech Republic (Dejmek et al. 1999; Dejmek et al.

2000). In a recent article by Le et al. 2012, authors found significant positive associations in the third trimester for highest quartiles of exposure and SGA in Detroit, Michigan (Le et al. 2012). Mannes et al. 2005 also found weak associations between PM_{10} and SGA and with $PM_{2.5}$ in Australia (Mannes et al. 2005). However another Australian study completed by Hansen et al. 2007 found no association between PM_{10} and SGA in any trimester (Hansen et al. 2007). The annual ambient average concentration for diesel engine emissions for our study was much lower than for the above-mentioned studies, which used air monitoring data to estimate concentrations for shorter durations of gestation (months, trimesters). Thus, it is difficult to make comparisons to the literature with the diesel engine emissions results obtained in our study for this reason.

A possible limitation of this research is exposure misclassification due to using maternal residence at birth for mothers who may have moved during pregnancy; however, this is likely to be nondifferential bias. Lupo et al. found that maternal residential mobility did not affect exposure assessment in Texas (Lupo et al. 2010). U.S. NATA data contain annual ambient average pollutant concentrations for census tracts across the nation. This means that the modeled data cannot distinguish variations of exposure during seasons of the year or even trimesters. U.S. NATA data are limited by uncertainties such as emission characterization, meteorological characterization, model formulation and methodology, monitoring uncertainties, and uncertainties in background concentrations. The U.S. EPA assesses the overall confidence in the exposure assessment by looking at estimates of emissions, ambient concentrations, and exposure concentrations (U.S. EPA 2009). Estimates for benzene have a higher overall confidence than those for PAHs, naphthalene, and diesel

engine emissions, which the U.S. EPA classified as medium overall confidence. It has been reported that in Texas these modeled estimates are generally underestimates as compared to air monitoring data (Lupo and Symanski 2009) as well as by the EPA stating in its 2002 model-to-monitor comparison that benzene may be underestimated by 23% (U.S. EPA 2010b). Another possible limitation of this study is that date of last menstrual period (LMP) was taken from the birth certificate to calculate gestational age. It is possible that some nondifferential misclassification of SGA may have occurred which would skew the results toward the null. Additionally, this study could not account for variations in indoor exposure to air toxics as well as dietary intake of PAHs. It is important to remember that not all SGA infants are growth restricted. Many SGA infants are "constitutionally small" due to infant and maternal factors such as female sex, maternal race, parity, or body mass. Infants may be defined as SGA because they are constitutionally small, meaning genetically small, or they may be infants who have intrauterine growth restriction (IUGR), or who are both constitutionally small and growth-restricted.

There are many strengths of this study. There are a large number of study subjects, 71,032, which gives this study considerable statistical power. The use of hierarchical modeling is an important strength of this study because it can handle random effects from the grouping variable, Greater Houston Area census tracts.

Conclusion

Overall, there were no significant associations between the four air toxics of interest and SGA. This is one of the first studies to look at the association of SGA and air toxics in

the state of Texas. Further studies looking at the association of air toxics and SGA should be completed.

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Table 1. Distribution of Ambient Levels of Combustion Pollutants in the Greater Houston Area, 2002 (n = 71,032 infants in 887 Census Tracts)

	Mean	Minimum	25th Percentile	Median	75th Percentile	Maximum
∑ c-PAHs[a]	12.56	0.97	7.76	11.18	15.35	273.23
Naphthalene[a]	58.16	13.19	41.48	53.31	69.23	365.47
Benzene[b]	1.59	0.21	1.16	1.44	1.82	8.01
Diesel Engine Emissions[b]	2.33	0.46	0.46	1.79	2.39	25.32

[a] ng/m^3

[b] $\mu g/m^3$

Table 2. Crude Odd Ratios (ORs) (95% CI) for the Associations between Demographic Characteristics and SGA in Full-Term, Singleton Infants Born in the Greater Houston Area, 2002 (n = 71,032)

Characteristics		Full-Term Singleton Infants (%) n= 71,032	SGA Term Infants (%) n = 6514	OR (95% CI)
Infant Sex	Female	49.24	47.80	Reference
	Male	50.76	52.20	1.07 (1.01 - 1.12)
Maternal Race	Non-Hispanic White	32.97	23.83	Reference
	Other	5.74	7.74	1.99 (1.79 - 2.21)
	Black	15.31	24.69	2.45 (2.27 - 2.63)
	Hispanic	45.54	43.29	1.35 (1.26 - 1.43)
Maternal Education	More than High School	36.90	29.51	Reference
	High School	28.27	30.43	1.38 (1.30 - 1.48)
	Less than High School	33.29	38.39	1.49 (1.40 - 1.59)
Maternal Smoking	No	94.75	91.25	Reference
	Yes	5.09	8.55	1.87 (1.71 - 2.06)
Maternal Alcohol Use	No	98.89	98.66	Reference
	Yes	0.94	1.14	1.24 (0.97 - 1.58)
Maternal Age	20 - 24 years	26.95	30.64	Reference
	≤ 19 years	11.52	9.64	1.40 (1.27 - 1.54)
	25 - 34 years	49.27	41.65	1.39 (1.30 - 1.47)
	≥ 35 years	12.26	18.07	0.75 (0.69 - 0.80)
Maternal Weight Gain	20 - 35 lbs.	47.72	49.94	Reference
	< 20 lbs.	17.10	22.47	0.77 (0.73 - 0.83)
	> 35 lbs.	26.40	18.31	1.54 (1.43 - 1.65)
Number of Prenatal Visits	11 - 15	35.94	31.75	Reference
	0 - 7	14.36	17.79	1.45 (1.35 - 1.57)
	8 - 10	29.37	30.03	1.17 (1.10 - 1.25)
	more than 15	17.63	16.93	1.10 (1.01 - 1.18)
Parity	1 or more	60.86	50.69	Reference
	Nulliparous	38.26	48.31	1.58 (1.50 - 1.67)
Marital Status	Married	67.41	56.66	Reference
	Not Married	32.53	43.28	1.66 (1.58 - 1.75)
Birth Season	Warm (April - Sept)	50.63	50.46	Reference
	Cool (Oct - March)	49.37	49.54	1.01 (0.96 - 1.06)
Maternal Nativity	U.S. Born	60.72	61.30	Reference
	Foreign Born	38.83	38.18	0.97 (0.92 - 1.02)
Median Census Tract Household Income	> $50,000	32.10	25.96	Reference
	$40,001 - 50,000	17.79	18.05	1.27 (1.16 – 1.39)
	$30,001 - 40,000	25.15	26.44	1.33 (1.23 – 1.44)
	≤ $30,000	24.95	29.54	1.54 (1.42 – 1.66)

Table 3. Crude and Adjusted Odds Ratios (ORs) (95% CI) for the Associations between Annual Census Tract Levels of Air Pollution and SGA.

	Crude		Adjusted†	
POLLUTANT	OR	95% CI	OR	95% CI
∑ c-PAHs[a]	1.08	1.05 - 1.11	1.01	0.97 - 1.05
Naphthalene[b]	1.02	1.01 - 1.03	1.00	0.99 - 1.01
Benzene[c]	1.08	1.04 - 1.13	1.01	0.97 - 1.05
Diesel Engine Emissions[d]	1.26	1.10 - 1.44	1.08	0.95 - 1.23

† Model adjusted for maternal race, maternal education, self-reported tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census-tract income

[a] per 10 ng/m^3 increase

[b] per 10 ng/m^3 increase

[c] per 1 μg/m^3 increase

[d] per 10 μg/m^3 increase

Table 4. Crude and Adjusted Odds Ratios (ORs) (95% CI) for the Associations between Annual Census-Tract Levels of Air Pollution by Reynold's Categories and SGA.

Crude Models

	∑ c-PAHs		Naphthalene		Benzene		Diesel Engine Emissions	
Exposure Category	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low	Referent		Referent		Referent		Referent	
Medium	1.10	1.02 - 1.19	1.09	1.01 - 1.18	1.13	1.05 - 1.22	1.05	0.97 - 1.13
High	1.23	1.11 - 1.36	1.20	1.08 - 1.33	1.22	1.10 - 1.35	1.14	1.03 - 1.26
Very High	1.21	1.08 - 1.36	1.19	1.06 - 1.34	1.22	1.09 - 1.37	1.22	1.08 - 1.36

Adjusted Models†

	∑c-PAHs		Naphthalene		Benzene		Diesel Engine Emissions	
Exposure Category	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low	Referent		Referent		Referent		Referent	
Medium	0.99	0.92 - 1.06	1.00	0.93 - 1.08	1.05	0.97 - 1.13	1.03	0.96 - 1.10
High	1.00	0.91 - 1.10	1.01	0.91 - 1.11	1.01	0.91 - 1.12	1.00	0.91 - 1.10
Very High	1.04	0.86 - 1.07	0.98	0.88 - 1.10	1.02	0.91 - 1.15	1.00	0.90 - 1.11

†Model adjusted for maternal race, maternal education, self-reported tobacco use, maternal age, number of prenatal visits, marital status, maternal weight gain, and median census-tract income

∑ c-PAHs (ng/m^3): low (<7.82), medium (7.82 - 15.38), high (15.39 - 21.07), very high (>21.07)

Naphthalene (ng/m^3): low (<41.54), medium (41.54 - 69.26), high (69.27 - 90.92), very high (>90.92)

Benzene ($\mu g/m^3$): low (<1.15), medium (1.15 - 1.82), high (1.83 - 2.43), very high (>2.43)

Diesel Engine Emissions ($\mu g/m^3$): low (<1.41), medium (1.41 - 2.40), high (2.41 - 3.78), very high (>3.78)

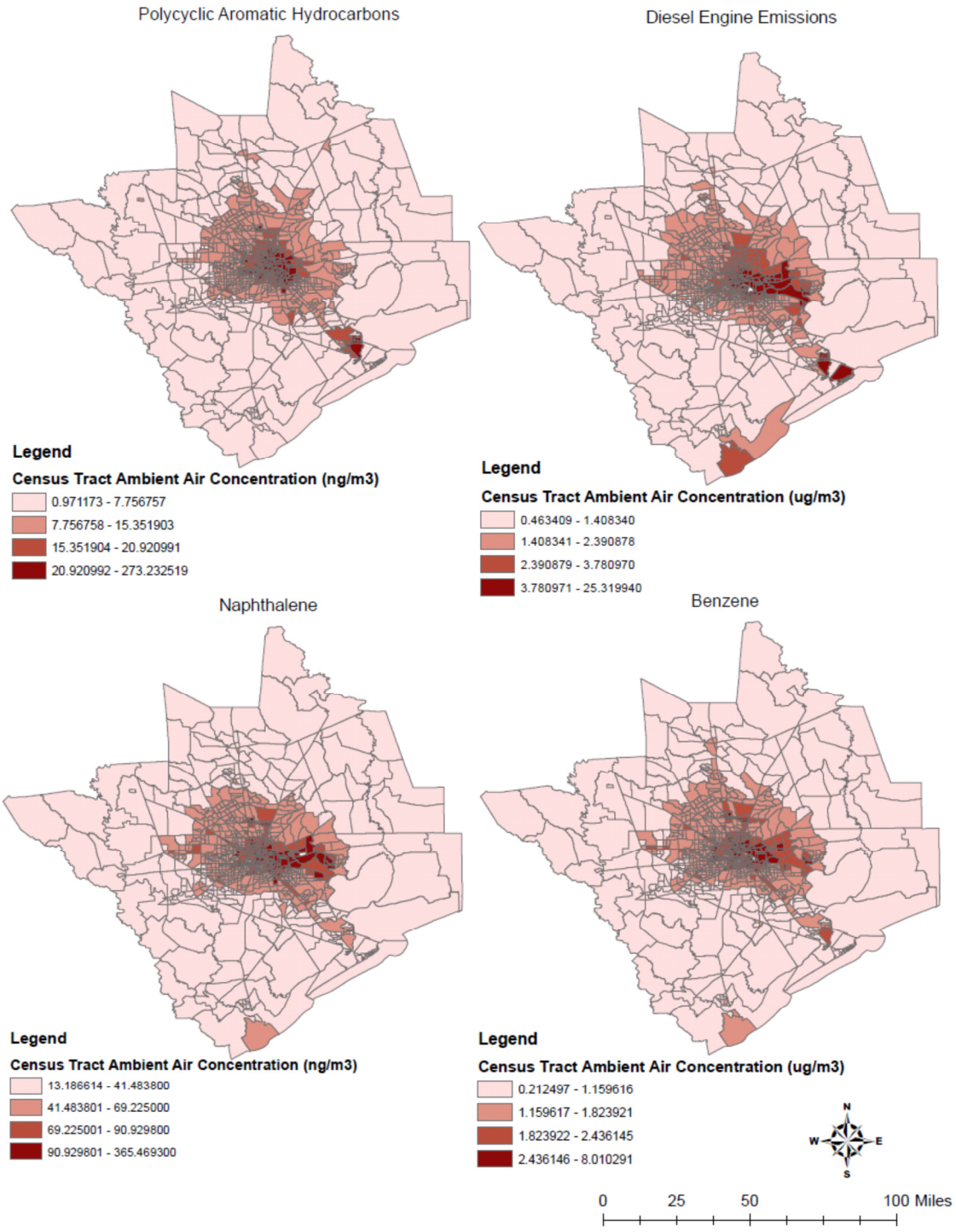

Figure 1. Distribution of Annual Ambient Census Tract Estimates of Each Pollutant in the Greater Houston Area, 2002

CHAPTER III: ASSOCIATION BETWEEN AMBIENT LEVELS OF POLYCYCLIC AROMATIC HYDROCARBONS AND SMALL FOR GESTATIONAL AGE HISPANIC INFANTS BORN ALONG THE UNITED STATES-MEXICO BORDER

Abstract

Background Few studies have looked at the association between polycyclic aromatic hydrocarbons (PAHs) and adverse birth outcomes and no studies have determined if there is an association in vulnerable populations along the United States (U.S.)-Mexico border. Little is known about the important window of susceptibility for exposures to this complex group of chemicals and infants born small for their gestational age (SGA).

Objectives This study examined whether trimester-specific exposure to PAHs during pregnancy was associated with SGA in Hispanics of El Paso County, Texas.

Methods Ambient air measurements for carcinogenic PAHs (c-PAHs), benzo[a]pyrene, and naphthalene were obtained from the U.S. EPA Air Quality System (AQS) Data Mart for the years 2004 - 2007. Birth certificates for infants born in 2005 – 2007 were obtained from the Texas Department of State Health Services (TX DSHS) for El Paso County, Texas. PAH exposures were estimated for each trimester and for 9-months of pregnancy for each mother. Crude and adjusted odds ratios (AORs) of SGA for trimester-specific pollutant and 9-month exposure data were estimated using logistic regression models.

Results Adjusted odds ratios (AORs) and 95% confidence intervals (CI) for increases of 5 ng/m^3 in c-PAHs, 1 ng/m^3 of benzo[a]pyrene, and 100 ng/m^3 in naphthalene during the third trimester of pregnancy were 1.02 (0.97 – 1.07), 1.03 (0.96 – 1.11), and 1.01 (0.97 – 1.06), respectively. Exposures in the other two trimesters and over the 9-month pregnancy period also showed no significant associations.

Conclusions These findings do not provide evidence of an association between trimester-specific or 9-month exposure to PAHs and SGA in El Paso County, Texas.

Keywords: Air pollution, Small for Gestational Age, Polycyclic Aromatic Hydrocarbons, Pregnant Women, Prenatal Development, Child Health, Hispanics

Introduction

There are a limited number of epidemiological studies that have explored associations between polycyclic aromatic hydrocarbons (PAHs) and adverse birth outcomes.[1-4] PAHs are complex mixtures of chemicals that are formed during incomplete burning of organic substances. PAHs can be in a gaseous form or adsorbed onto small particulate matter depending on their molecular properties. Sources of PAHs include vehicle exhaust, tobacco smoke, agricultural burning, residential wood burning, municipal and industrial waste incineration, and hazardous waste sites. Inhalation of PAHs adsorbed onto fine particulate matter (PM) is one major route of exposure.[5] Similar to concerns about PM, maternal exposure to PAHs during pregnancy may impair fetal growth and increase the risk of infants who are born small for their gestational age.

In addition to questions about which air pollutant might increase risk for SGA, the critical window of susceptibility during pregnancy regarding air pollutant exposure has been an important methodological challenge in studies examining fetal development.[6] The first trimester is when placental attachment and organ development occurs while the third trimester is when the growth rate is the highest for the fetus. Exposures to air pollution during pregnancy may leave the fetus vulnerable; however, only one study has looked at which gestational period is most susceptible to carcinogenic-PAHs (c-PAHs).[7] Most studies regarding PAHs and adverse birth outcomes such as SGA, preterm births, lower birth weight, and small head circumference have been conducted in Europe, Northeastern United States, and Western United States.[1-4,8]

There has been no evaluation of the associations between PAHs and adverse birth outcomes in vulnerable populations especially among populations along the United States (U.S.)-Mexican Border. El Paso County is a unique geographic location to study air pollutants such as PAHs and adverse birth outcomes. A recent study by De La Torre-Rocha and colleagues studied soil-borne PAHs in El Paso, Texas.[9] They found that light PAHs such as naphthalene are distributed in soil evenly across major distances while heavier PAHs concentrations are more prominent around soils closer to industry. El Paso had high concentrations of PAHs in soil near the major interstate highway and downtown. PAH concentrations may be affected by sources from El Paso's sister city in Mexico, Ciudad Juarez. These sources include maquiladoras, brick kilns, and the burning of tires and wood for heating and cooking.[9] The U.S. Environmental Protection Agency (EPA) classified El Paso County as having moderate nonattainment for particulate matter up to 10 micrometers in size (PM_{10}).[10] Since PAHs may adsorb onto particulate matter, PAH concentrations may be elevated.

The aim of this population-based study was to examine whether trimester-specific exposure to PAHs during pregnancy was associated with SGA infants born to Hispanic mothers in El Paso County, Texas. Pollutants examined included carcinogenic PAHs (c-PAHs), benzo[a]pyrene (a major component of c-PAHs), and naphthalene.

Methods

Study Subjects

A population-based study was conducted based on Texas Birth Certificate records collected by the Texas Department of State Health Services (TX DSHS) of all live, full-term (>37 completed weeks of gestation), singleton births registered in El Paso County, Texas for the years 2005 – 2007. TX DSHS excluded infants with birth defects because many infants with birth defects are growth restricted which is presumed to be secondary to the birth defect. The study population was restricted to Hispanics who comprise more than 75% of the population in El Paso County.[11] The total number of infants born in El Paso County during the study period without birth defects was 52,347. We excluded infants if the birth records were missing geocoded maternal residence at birth (n=12,841) or the mother lived outside of El Paso County (n=141). Other exclusions included non-singleton infants (n = 988), non-Hispanics (n= 4262), those missing birth weight (n=1), infants less than 37 weeks gestation (n= 3212), and those with extreme values for gestational age and birth weight (n= 119). The number of live, full-term, Hispanic, singleton infants born in 2005 - 2007 for this study was 30,783 (58.80% of original cohort).

The Institutional Review Boards for the Texas Department of State Health Services (TX DSHS) and the University of Texas Health Science Center at Houston approved this study.

Classification of Small for Gestational Age (SGA)

Infants with SGA were identified using information available on birth certificate records. Briefly, a SGA case was an infant whose weight was below the 10th percentile for gestational age and sex based on the United States birth weight centile for gestational age and sex in 1999 – 2000.[6,12,13] Gestational age was determined by examining (1) gestational age calculated from the mother's last menstrual period (LMP) and (2) gestational age at birth as reported by the physician who delivered the infant. If the absolute difference between the clinical estimates of gestational age and gestational age calculated from LMP was more than 2 weeks, the clinical estimate of gestational age was used to determine SGA (n = 2372, 7.71%). If the gestational age calculated from LMP was missing, the obstetric estimate was used (n = 906, 2.94%) and vice versa (n = 8, 0.03%).

Exposure Assessment for PAHs

The PAHs used in analyses represent the sum of the seven carcinogenic PAHs (c-PAHs). These PAHs include benzo[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenzo[a,h]anthracene, and indeno[1,2,3-cd]pyrene. Additionally, separate analyses for benzo[a]pyrene and naphthalene were conducted. PAHs are captured on a polyurethane foam (PUF) cartridge that is analyzed by gas chromatography/mass spectrometry (GC/MS) according to U.S. EPA Compendium Method TO-13A every 6 days.[14] The mother's residence at the time of delivery (using geocoded

addresses made available by the TX DSHS) was linked to the available air monitoring data from the U.S. EPA Air Quality System (AQS) (EPA Site #: 48-141-0053) by geographic information systems (GIS).[15] PAH concentrations were given in units of ng/m^3 by the U.S. EPA AQS. ArcView (Version 9.3, Environmental Systems Research Institute, Inc., Redlands, CA) was used to map maternal residence. Mothers' PAH exposures were estimated for each trimester of pregnancy and 9-month exposure period. This study defined the first trimester as LMP through 97 days, the second trimester as days 98 through 188, the third trimester as days189 through 280, and 9-month exposure as LMP through 280 days of pregnancy.

Statistical Analyses

The mean and standard deviation for each PAH exposure metric was calculated and the correlation between exposure metrics using Pearson correlation coefficients was examined. Crude and adjusted associations of continuous PAH exposure on the odds of SGA were estimated using logistic regression models. Models were adjusted for maternal age (≤19 years, 20 – 24 years, 25 – 34 years, ≥ 35 years), maternal education (less than high school, high school, more than high school), maternal smoking (non-smoker, smoker prior, but stopped early (first or second trimester), smoked through pregnancy), marital status (married, not married), and parity (nulliparous, 1 or more births) which were obtained from birth certificates. Models also included a variable for birth season (warm: April through September, cool: October through March) to control for the possible seasonal effects. Analyses stratified by maternal age, maternal education, maternal weight gain, and birth

season were also conducted to explore the possibility of effect measure modification. Odds ratios (ORs) and 95% confidence intervals (CI) are reported. All statistical analyses were performed using SAS (Version 9.3, SAS Institute, Inc., Cary, NC).

Results

Descriptive Statistics for PAHs

Monthly levels (ng/m^3) of c-PAHs, benzo[a]pyrene, and naphthalene from January 2004 through December 2007 are shown in Figures 1- 3. Highest concentrations of c-PAHs and benzo[a]pyrene are found during the winter months (January, February, November, and December). The Pearson correlation coefficient between c-PAHs and benzo[a]pyrene was high (0.99) because benzo[a]pyrene is component of c-PAHs. There was little seasonal variation for naphthalene. Table 1 contains descriptive statistics of PAHs for each exposure period. Mean trimester exposures were similar to the 9-month exposure level for all PAHs (~5.5 ng/m^3 for c-PAHs, ~0.60 ng/m^3 for benzo[a]pyrene, and ~330 ng/m^3 for naphthalene). The correlations between the trimester-level exposures and the corresponding 9-month exposure were high and mostly positive for the year 2005 (Table 2). Other years show correlations that are mixed between trimester-level exposures as well as between trimester-level exposures and corresponding 9-month exposures.

Associations between PAHs and SGA

Demographic characteristics of the study population are provided in Table 3. Among the 30,783 Hispanic infants in this cohort, 3420 or 11.1% were born SGA from 2005 - 2007.

Over three quarters of the population reported "Mexican" as their Hispanic origin. In simple logistic regression models, our results suggest greater odds of SGA for mothers who had high school education (OR = 1.14, 95% CI = 1.04 – 1.24) and for mother who had less than high school education (OR = 1.13, 95% CI = 1.03 – 1.22) compared to those mothers with more than a high school education; greater odds of SGA for mothers who smoked through pregnancy (OR = 1.60, 95% CI = 1.08 – 2.39) and reduced odds of SGA for mothers who quit earlier in pregnancy (OR = 0.88, 95% CI = 0.66 – 1.18) compared to mothers who were non-smokers; greater odds of SGA for mothers less than 19 years of age (OR = 1.24, 95% CI = 1.12 – 1.37) but reduced odds of SGA for mothers 25 - 34 years of age (OR = 0.73, 95% CI = 0.67 – 0.79) or 35 years of age and older (OR = 0.87, 95% CI = 0.77 – 0.99) compared to mothers 20 to 24 years of age; greater odds of SGA for mothers who are nulliparous (OR = 1.42, 95% CI = 1.33 – 1.53); and finally, greater odds of SGA for mothers who are not married compared to mothers who are married (OR = 1.35, 95% CI = 1.26 – 1.45).

The results from the multiple logistic regression analyses examining associations between PAHs and SGA are shown in Table 4. There were slightly reduced odds of SGA for the first and second trimester as well as the 9-month exposure period per 5 ng/m^3 increase of c-PAHs (AOR = 0.97, 95% CI = 0.92 – 1.02; AOR = 0.96, 95% CI = 0.92 – 1.01, AOR = 0.94, 95% CI = 0.86 – 1.02, respectively). The third trimester showed slightly greater odds of SGA per 5 ng/m^3 increase in c-PAHs; however, results were not significant (AOR = 1.02, 95% CI = 0.97 – 1.07). The associations for benzo[a]pyrene and naphthalene demonstrated similar results to c-PAHs. There were reduced odds of SGA for the first and second trimester in addition to the 9-month exposure period per 1 ng/m^3 increase in benzo[a]pyrene

(AOR = 0.96, 95% CI = 0.88 – 1.03; AOR = 0.95, 95% CI = 0.89 – 1.02; AOR = 0.91, 95% CI = 0.79 – 1.05). The third trimester demonstrated a positive association with SGA per 1 ng/m^3 increase of benzo[a]pyrene, but results were not significant (AOR = 1.03, 95% CI = 0.96 – 1.11). Naphthalene exposure (per 100 ng/m^3 increase) showed reduced odds of SGA for the first and second trimester and the 9-month exposure period (AOR = 0.97, 95% = 0.92 – 1.02, AOR = 0.98, 95% CI = 0.94 – 1.02, AOR = 0.97, 95% CI = 0.91 – 1.04). The third trimester demonstrated a positive association with SGA per 100 ng/m^3 increase of naphthalene; however, the effect was minimal and non-significant (AOR = 1.01, 95% CI = 0.97 – 1.06). Stratified analyses by maternal age, maternal education, maternal weight gain, marital status and birth season did not appreciably change odds ratios for the association between air pollution and SGA (results not shown).

Discussion

This study examined the associations between trimester-specific and 9-month levels of c-PAHs, benzo[a]pyrene, and naphthalene and SGA in Hispanic newborns born in El Paso County, Texas in 2005 - 2007. After controlling for maternal factors, our findings do not provide evidence of an association between maternal exposure to ambient air levels of PAHs and SGA during any pregnancy period in this population. This is the first study to examine associations between air pollutants and an adverse birth outcome in El Paso County, a unique geographic area with a predominantly Hispanic population and multiple sources of PAHs.

The findings of this study are consistent with another study that reported no association between PAH exposure and SGA in Hispanics. Choi and colleagues conducted a

cohort study of African-American and Dominican mother-newborn pairs from New York City using personal monitoring during the third trimester of pregnancy.[1] They observed a 2-fold increase in the risk of symmetric IUGR among full-term African-American infants ($p<0.05$) per a 1 natural-log (ln) increase in prenatal PAH exposure, but no association among Dominicans although the mean exposure for PAHs was similar between the two groups.[1] Choi et al. attributed reduced IUGR risk in Dominicans to healthier diets and a strong social support network compared to the African Americans in their study.[1] Although there was no information from the birth certificate data regarding diet in our study, there was information regarding social support via the marital status variable. However, there was no evidence of effect measure modification by marital status upon stratified analyses in our study.

Few studies have examined the associations between ambient air pollution and SGA during specific pregnancy periods. Our study found slightly higher odds of SGA with exposures to c-PAHs, benzo[a]pyrene, and naphthalene in the third trimester; however, the results were not significant. In the Czech Republic, Dejmek et al. found an elevated association between the highest level tertile of c-PAHs (> 20 ng/m^3) and IUGR in the first gestational month (AOR = 2.39, 95% CI = 1.01 – 5.65) in Prachatice, a district that is known to have low concentrations of particulate matter.[2] However, no other pregnancy period was associated with IUGR. We completed similar analyses using our 95th percentile of c-PAHs (>17.4 ng/m^3) in the first trimester and found no significant associations with SGA (results not shown).

Supporting the results from our study, Bobak found in his national Czech Republic study that intrauterine growth restriction (IUGR), defined as <10th percentile of birth weight for gestational age and sex, was not associated with total suspended particulates (TSP) during any pregnancy period.[16] Inhalable particles were not monitored in the Czech Republic; thus, this may explain why Bobak found no associations. Other studies found significant, but weak associations between SGA and PM in certain pregnancy periods. Mannes et al. found that ambient levels of PM_{10} ($\mu g/m^3$) and $PM_{2.5}$ ($\mu g/m^3$) in the second trimester of pregnancy had a small but statistically significant effect on SGA (defined as greater than two standard deviations below the mean birth weight according to gestational age) for infants born in Sydney, Australia (AOR=1.01, 95% CI=1.00-1.04; AOR=1.03, 95% CI=1.01-1.05, per unit increase in pollutant concentration, respectively).[17] In a recent article by Le et al. 2012, the authors found a positive association in the third trimester for PM_{10} (> 35 $\mu g/m^3$) and term SGA (infants whose birth weights fell below the 10th percentile by sex and gestational week between ages 37 to 42 weeks) to be significant (AOR = 1.22, 95% CI = 1.03 – 1.46).[18]

A strength of this study was that it was restricted to Hispanics, an understudied and susceptible population and it had a large sample. Another strength of this study was the ability to control for potential individual-level confounders such as maternal age, maternal nativity, marital status and others. A limitation of this study is that there was only a single monitoring station for the entire county measuring PAHs. For this reason, there may be nondifferential misclassification of exposure. The Texas Commission on Environmental Quality (TCEQ), which is the responsible agency for conducting ambient air monitoring in the state, has only six monitors in five counties measuring PAH levels and this limits

assessments that can be made with respect to their effects on adverse birth outcomes. Additionally further studies should include PM and PAHs in the same model since PM influences the transport and penetration of PAHs from the ambient air to a potential mother. Lastly, this study was limited to information available from birth certificates; thus, no information regarding dietary intake or indoor and occupational exposures associated with PAHs were available.

Conclusion

This is the first study looking at adverse birth outcomes and air pollution in a vulnerable population along the U.S.-Mexico Border. This study found no evidence of an association between trimester-specific and 9-month exposure levels of PAHs and SGA among infants born in El Paso County, Texas. Further epidemiological studies should look at the association between air pollution and SGA in the Hispanic population along the U.S.-Mexico border.

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Table 1. Mean, Median, Range and Percentile Distribution for Exposure Estimates (ng/m^3) of Ambient Levels of c-PAHs, Benzo[a]pyrene, and Naphthalene, March 2004 – December 2007 (n = 30,783)

	c-PAHs				*Benzo[a]pyrene*				*Naphthalene*			
	Trimester 1	Trimester 2	Trimester 3	9-months	Trimester 1	Trimester 2	Trimester 3	9-months	Trimester 1	Trimester 2	Trimester 3	9-months
Minimum	1.98	1.8	1.8	3.06	0.15	0.15	0.15	0.26	207.89	206.07	206.07	235.06
5th percentile	2.3	1.99	1.99	3.47	0.15	0.15	0.15	0.31	235.28	221.94	223.6	272.24
25th percentile	2.95	2.73	2.61	4.07	0.19	0.18	0.18	0.42	281.8	273.05	267.12	299.02
Median	3.8	3.59	3.75	4.84	0.38	0.37	0.35	0.5	312.83	311.1	303.65	318.32
75th percentile	7.02	6.86	6.94	6.06	0.82	0.8	0.82	0.62	387.61	397.07	398.23	365.29
95th percentile	17.4	16.73	16.42	9.5	2.29	2.1	2.1	1.11	512.92	498.06	498.06	449.46
Maximum	19.6	19.86	19.86	9.7	2.51	2.6	2.6	1.13	550.31	564.89	564.89	469.42
IQR	4.07	4.13	4.33	1.98	0.63	0.62	0.64	0.2	105.82	124.02	131.11	66.27
Mean	5.73	5.49	5.53	5.64	0.61	0.59	0.59	0.6	339.33	334.33	331.04	336.01
Standard Deviation	4.17	4.22	4.2	2.06	0.58	0.58	0.58	0.27	78.91	83.61	85.41	53.17

Table 2. Pearson Correlation Coefficients between Trimester-Specific and Nine-Month Exposures to c-PAHs, Benzo[a]pyrene, and Naphthalene for Infant Birth Year (n = 30,783)

2005

	Benzo(a)pyrene				Naphthalene				c-PAHs			
	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months
trimester 1	1.000				1.000				1.000			
trimester 2	-0.175	1.000			-0.295	1.000			-0.272	1.000		
trimester 3	-0.678	-0.257	1.000		-0.087	0.391	1.000		-0.619	-0.239	1.000	
9-months	-0.290	0.288	0.685	1.000	0.091	0.713	0.864	1.000	-0.345	0.144	0.810	1.000

2006

	Benzo(a)pyrene				Naphthalene				c-PAHs			
	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months
trimester 1	1.000				1.000				1.000			
trimester 2	-0.021	1.000			0.255	1.000			-0.193	1.000		
trimester 3	-0.626	-0.071	1.000		-0.051	0.263	1.000		-0.628	-0.053	1.000	
9-months	0.268	0.641	0.176	1.000	0.642	0.791	0.543	1.000	0.269	0.652	0.190	1.000

2007

	Benzo(a)pyrene				Naphthalene				c-PAHs			
	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months	trimester 1	trimester 2	trimester 3	9-months
trimester 1	1.000				1.000				1.000			
trimester 2	-0.074	1.000			-0.227	1.000			-0.086	1.000		
trimester 3	-0.889	0.044	1.000		-0.300	-0.012[a]	1.000		-0.864	0.051	1.000	
9-months	0.986	0.881	0.095	1.000	0.302	0.585	0.496	1.000	0.069	0.871	0.155	1.000

Correlation coefficients are significantly different from 0, $p < 0.0001$ except [a] $p = 0.21$

Table 3. Crude Odd Ratios (ORs) (95% CI) for the Associations between Demographic Characteristics of Hispanic Infants Born in El Paso County and SGA, 2005-2007 (n = 30,783)

Characteristics		Full-Term Singleton Infants (%) n= 30,783	SGA Term Infants (%) n = 3,420	OR (95% CI)
Infant Sex	Female	49.52	48.51	Reference
	Male	50.48	51.49	1.05 (0.98 - 1.12)
Maternal Education	More than High School	39.36	36.78	Reference
	High School	26.48	27.75	1.14 (1.04 - 1.24)
	Less than High School	34.16	35.44	1.13 (1.03 - 1.22)
Maternal Smoking	Non-Smoker	97.43	97.22	Reference
	Smoked Prior, Stopped Early	1.67	1.49	0.88 (0.66 - 1.18)
	Smoked Through Pregnancy	0.57	0.85	1.60 (1.08 - 2.39)
Maternal Age	20 - 24 years	30.11	32.89	Reference
	≤ 19 years	16.63	21.87	1.24 (1.12 - 1.37)
	25 - 34 years	43.32	35.61	0.73 (0.67 - 0.79)
	≥ 35 years	9.94	9.62	0.87 (0.77 - 0.99)
Parity	1 or more	63.41	55.91	Reference
	Nulliparous	36.58	44.09	1.42 (1.33 - 1.53)
Marital Status	Married	57.28	50.64	Reference
	Not Married	42.72	49.36	1.35 (1.26 - 1.45)
Season of Birth	Warm (April - September)	50.78	50.61	Reference
	Cool (October - March)	49.22	49.39	1.01 (0.94 - 1.08)

Table 4. Crude and Adjusted Odds Ratios (ORs) (95% CI) for the Associations between SGA and PAHs by Gestational Period

	OR	95% CI	AOR[d]	95% CI
c-PAHs[a]				
First Trimester	0.98	0.93 – 1.02	0.97	0.92 – 1.02
Second Trimester	0.96	0.92 – 1.01	0.96	0.92 – 1.01
Third Trimester	1.01	0.97 – 1.06	1.02	0.97 – 1.07
9-months	0.94	0.86 – 1.02	0.94	0.86 – 1.02
Benzo[a]pyrene[b]				
First Trimester	0.96	0.91 – 1.03	0.96	0.88 – 1.03
Second Trimester	0.95	0.89 – 1.01	0.95	0.89 – 1.02
Third Trimester	1.02	0.96 – 1.09	1.03	0.96 – 1.11
9-months	0.91	0.80 – 1.04	0.91	0.79 – 1.05
Naphthalene[c]				
First Trimester	0.97	0.93 – 1.02	0.97	0.92 – 1.02
Second Trimester	0.98	0.94 – 1.02	0.98	0.94 – 1.02
Third Trimester	1.01	0.97 – 1.05	1.01	0.97 – 1.06
9-months	0.97	0.91 – 1.04	0.97	0.91 – 1.04

[a] per 5 ng/m^3 increase

[b] per 1 ng/m^3 increase

[c] per 100 ng/m^3 increase

[d] model adjusted for maternal age, maternal education, maternal smoking status, marital status, parity, and season of birth

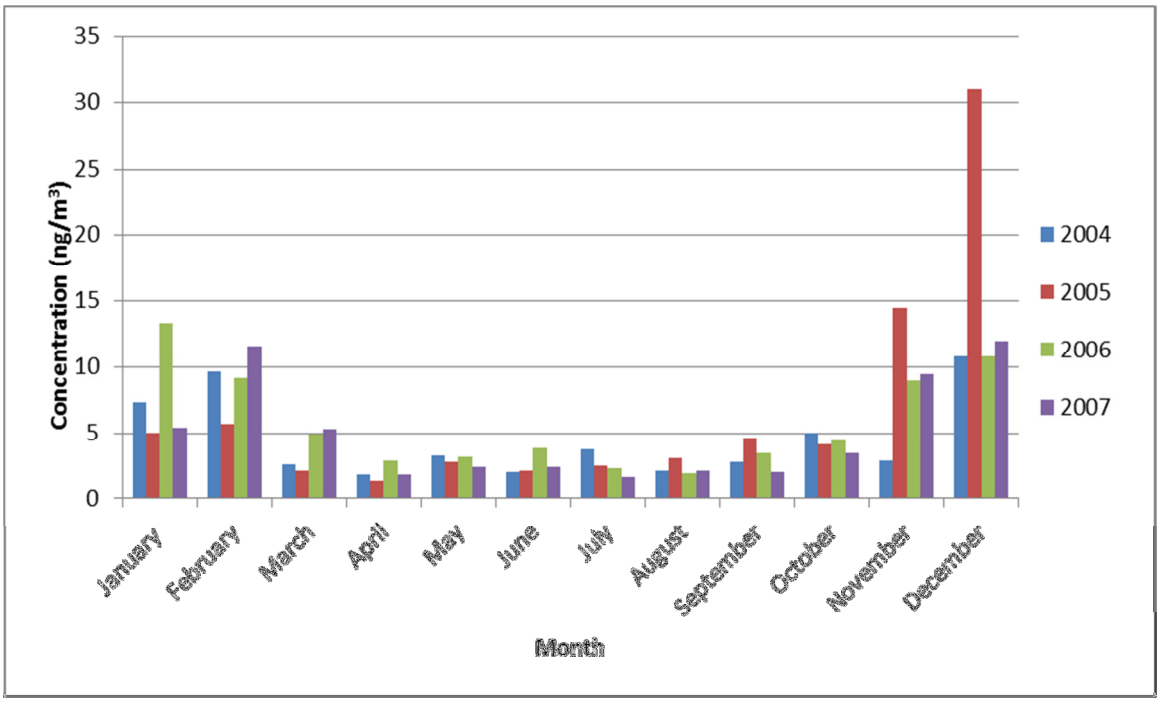

Figure 1. Monthly c-PAHs Concentrations (ng/m^3), 2004 - 2007

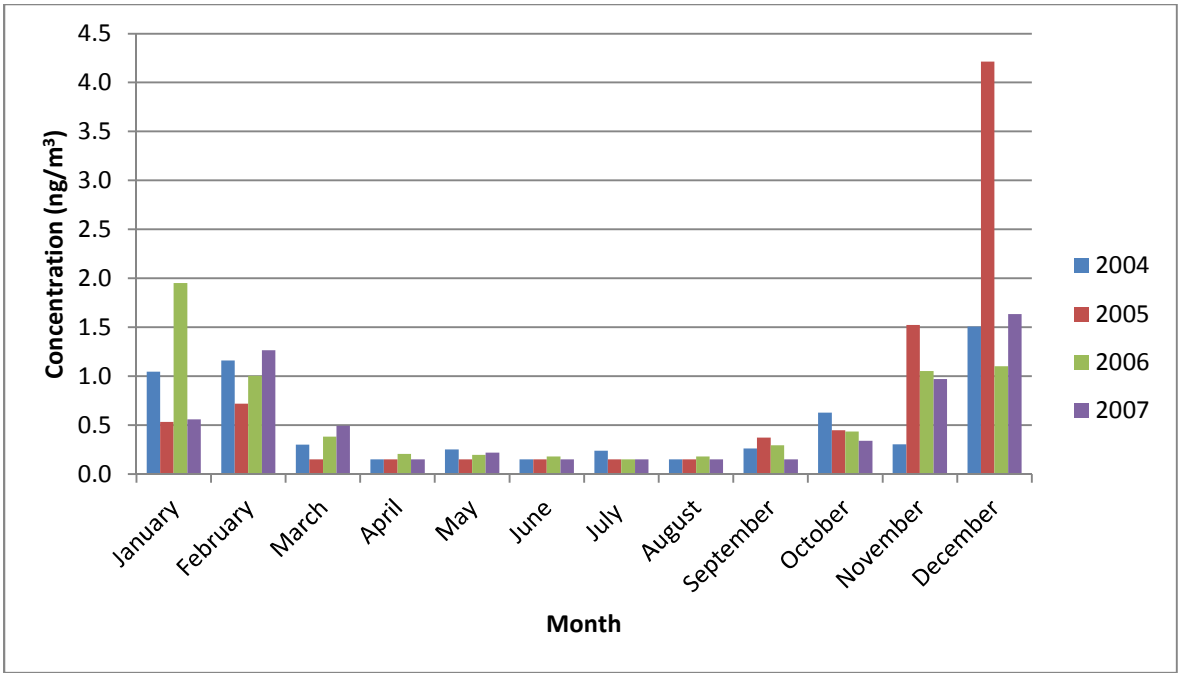

Figure 2. Monthly Benzo[a]pyrene Concentrations (ng/m^3), 2004 - 2007

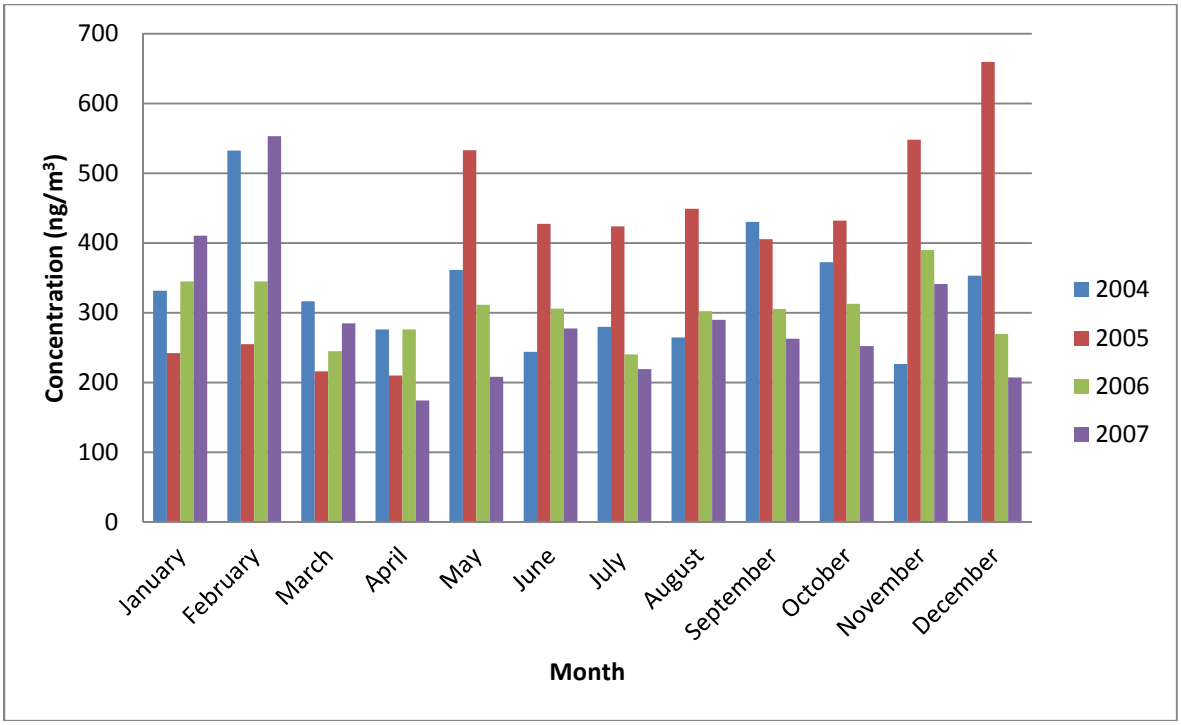

Figure 3. Monthly Naphthalene Concentrations (ng/m^3), 2004 - 2007

CHAPTER IV: ASSOCIATIONS BETWEEN TRAFFIC-RELATED AIR POLLUTION AND SMALL FOR GESTATIONAL AGE INFANTS IN HARRIS COUNTY, TEXAS, 2006

Abstract

Background Traffic-related air pollution exposure is influenced by residential proximity to roadways. There are positive associations between traffic-related air pollutants and SGA found in the epidemiological literature, but no study has been completed in the United States.

Objectives The objective of this study was to assess the association between maternal residential proximity to traffic and SGA in Harris County, Texas, 2006, an area with a large network of roadways.

Methods Birth certificates for nearly 53,000 infants born in 2006 were obtained from the Texas Department of State Health Services (TX DSHS) for Harris County, Texas. Two measures of traffic-related air pollution exposure were constructed. The first metric used proximity from maternal residence at delivery to major roadways and the second relied on annual average daily traffic (AADT) counts on major roadways within a 228.6 m buffer of a mother's residence to create a distance-weighted traffic density (DWTD) metric. Associations of traffic-related air pollution exposure and SGA were examined using logistic regression adjusting for maternal characteristics and season of birth.

Results In simple logistic regression analyses there was a negative association with increasing distance from a maternal residence to the nearest a major roadway (Odds Ratio (OR)= 0.96; 95% Confidence Interval (CI) = 0.94 - 0.97) per 1000 m); however, once adjusted for covariates, this result was no longer significant (Adjusted Odds Ratio (AOR) = 0.98; 95% CI = 0.96 – 1.00). There was a positive association with SGA in simple logistic regression for the DWTD (OR = 1.03, 95% CI = 0.90 – 1.17) but when adjusted for covariates, there was a negative association (AOR = 0.96, 95% CI = 0.84 – 1.09). The study population lived on average about 1650 m away from a major roadway that resulted in difficulties using the DWTD metric.

Conclusions There is no evidence to suggest that maternal residence near major roadways is associated with SGA in Harris County, Texas.

Keywords
Air pollution, Small for Gestational Age, Traffic, Pregnant Women, Prenatal Development, Child health

Background

Motor vehicle emissions are complex mixtures of chemicals. Vehicles emit carbon dioxide (CO_2), carbon monoxide (CO), hydrocarbons, nitrogen oxides (NO_x), particulate matter (PM), and substances known as mobile-source air toxics (MSATs) [1]. MSATs include chemicals such as benzene, formaldehyde, acetaldehyde, 1,3-butadiene, acrolein, naphthalene, polycyclic organic matter (POM), and diesel exhaust [2]. Besides these traffic-related air pollutants, individuals living close to a roadway are exposed to more noise and light pollution [1]. Exposure to these toxicants during pregnancy, a highly susceptible period for the fetus, may increase the risk for adverse birth outcomes such as small for gestational age (SGA). SGA is defined as birth weight of an infant less than the tenth percentile for a given gestational age and sex [3,4]. It has been associated with neonatal morbidity and mortality, developmental delays, and increased risk in adulthood for diabetes and cardiovascular diseases [5-9].

Spatial variation of traffic-related air pollutants is important to exposure assessment as mothers residing nearer to heavy-trafficked roadways and freeways may be exposed to higher levels of the pollutants compared to those further away from the source. Surrogate measures, such as proximity to major roadways and a distance-weighted traffic density metric, have been applied to account for small-scale spatial variation in roadway exposures in studies of SGA outside of the United States [10-12]. A study completed in Vancouver, British Columbia, Canada, reported a positive significant association between maternal residences less than 50 m from a roadway and SGA (Adjusted Odds Ratio (AOR) = 1.26, 95% Confidence Interval (CI) = 1.07 – 1.49) [10]. Another study from Montreal, Quebec,

found increased odds of SGA for mothers who lived less than 200 m away from a highway (OR = 1.32, 95% CI – 1.05 – 1.66) [11]. Lastly, a Dutch study completed in Rotterdam, the Netherlands, the second largest city in the Netherlands, found an association at the highest quartile of distance weighted traffic density (DWTD) (over 1.2 million vehicles/24 hours*m) and SGA (AOR = 1.12, 95% CI = 0.78 – 1.59) and proximity to roadway (< 50 m) and SGA (AOR = 1.14, 95% CI = 0.77 – 1.68) [12]. No report has yet addressed associations between traffic-related air pollution and SGA in the United States.

Harris County, Texas, which is located within the Houston-Sugarland-Baytown metropolitan area, is the fifth largest metropolitan area in the United States [13], and has numerous interstates, federal and state highways, and toll ways. The aim of this study was to investigate the association between SGA and maternal exposure to traffic-related air pollutants using (1) distance-weighted traffic density (DWTD) and (2) maternal residential distance to major roadways of Harris County, Texas in 2006.

Methods

Study Subjects

A population-based study was conducted based on Texas Birth Certificate records collected by the Texas Department of State Health Services (TX DSHS) of all live, full-term (≥ 37 completed gestational weeks), singleton births registered in Harris County, Texas for the year 2006. Prior to making the data available, TX DSHS excluded infants with birth defects because many infants with birth defects are also growth restricted [7]. The total

number of infants born in Harris County, Texas in 2006 without birth defects was 72,010. The following exclusions were applied: birth records with missing geocoded maternal residence at birth (n = 1366), maternal residences not in Harris County (n = 9277), non-singleton infants (n = 2266), infants less than 37 weeks gestation (n = 6470) or with extreme values for gestational age and birth weight (n = 372), and maternal residences < 6 m from nearest roadways (n = 2). The number of live, full-term, singleton infants born in 2006 utilized in this study was 52,257 (72.57% of original cohort).

The Institutional Review Boards for the Texas Department of State Health Services (TX DSHS) and the University of Texas Health Science Center at Houston approved this study.

Small for Gestational Age (SGA) Classification

Infants with SGA were identified using information available on birth certificate records. SGA was defined as an infant whose weight is below the 10th percentile for gestational age and sex based on U.S. birth [3,4,14]. Gestational age was determined by examining either the gestational age calculated from the mother's last menstrual period (LMP) or gestational age at birth as reported by the physician who delivered the infant. If gestational age calculated from LMP was missing, then the clinical estimate was used (n = 1024, 1.96%) and vice versa (n = 13, 0.02%). The clinical estimate was used to determine SGA if the difference between the clinical estimates of gestational age and gestational age calculated from LMP was more than 2 weeks (n = 4154, 7.95%).

Exposure Assessment for Traffic-Related Air Pollutants Metric

Major roadways classified as MAF/TIGER Feature Class Codes (MFTCC) S1100 (primary roadways such as interstates) and S1200 (secondary roadways such as U.S., state, or county highways) in Harris County were retrieved from U.S. Census Bureau [15] and for each birth record distance in meters from the geocoded maternal residence to the nearest major roadway was computed. For the second exposure metric, annual average daily traffic (AADT) counts for interstate highways, U.S. highways, state highways, or county highway systems in Harris County for 2006 were obtained from the Texas Department of Transportation (TX DOT) and used to construct a distance-weighted traffic density (DWTD) metric. Briefly a 228.6 m, or 750 ft, radius buffer was constructed around each subject's home and then a model was used to estimate the dispersion of motor vehicle exhaust from the roadways within this buffer region [16]. This model was applied originally by Pearson al. (2000) and is based on a Gaussian probability distribution assuming that 96% of all motor vehicle exhaust pollutants disperse at 150 m from the roadway according to the following equation:

$$Y = \left(\frac{1}{0.4\sqrt{2\pi}}\right) \times \exp\left[\left(\frac{(-0.5)(\frac{D}{150})^2}{(0.4)^2}\right)\right]$$

where D is the shortest distance from the subject home to the street (m) and Y is the value used to weight the AADT count (number of vehicles/24 hours) on each street within a

subject's buffer[17]. The weighted AADT values for all streets within the buffer were then summed for each subject to yield the DWTD metric (number of vehicles/ 24 hours * m). ArcView (Version 9.3, Environmental Systems Research Institute, Inc, Redlands, CA) was used to map maternal residences, traffic counts, and major roadways in Harris County.

Statistical Analyses

Descriptive statistics were calculated for the exposure metrics that were applied in the study. The distance of maternal geocoded residence at birth from a major roadway was categorized as < 50, 51 – 100, 101 – 200, 200 – 300, and > 300 m. Crude and adjusted effects for each exposure metric on the odds of SGA infants were evaluated using logistic regression. Models were adjusted for maternal race/ethnicity (Non-Hispanic White, Other, Black, Hispanic), maternal age (≤19 years, 20 – 24 years, 25 – 34 years, ≥ 35 years), maternal education (less than high school, high school, more than high school), maternal smoking (non-smoker, smoker prior, but stopped early, smoked through pregnancy), marital status (married, not married), and parity (nulliparous, 1 or more births). Models included a variable for season of birth (warm: April through September, cool: October through March) to control for the possible seasonal effects. All covariates were obtained from birth certificate data. Stratified analyses were also conducted to explore the possibility of effect measure modification by maternal race, maternal age, maternal smoking, and season of birth. Estimated odds ratios (ORs) and 95% confidence intervals (CI) are reported. All statistical analyses were performed using SAS (Version 9.3, SAS Institute, Inc., Cary, NC).

Results

Demographic Characteristics

The study population consisted of 52,257 live, full-term, singleton infants and 5,289 SGA infants who were born in Harris County, Texas during 2006. The prevalence of SGA in this study population was 10.12%. The crude odds ratios (OR) and 95% CI for an association between demographic characteristics for the study population are presented in Table 1.

Descriptive Statistics

The descriptive statistics for distance from geocoded maternal residence to nearest roadway are found in Table 2. The mean (standard deviation) of DWTD metric was 1966.5 vehicles/24 hours * m (15,802 vehicles/24 hours * m). Geocoded maternal residences were on average 1650 m away from a major roadway. Using the DWTD metric proved to be difficult because of the long distances from maternal residences to the nearest roadways. For this reason, the DWTD exposure metric was dichotomized at the 95^{th} percentile. Results of the statistical analyses are reported using the dichotomized DWTD metric. There were few mothers in this study population (1.5%) who lived less than 50 m from a major roadway (Table 3).

Associations between Traffic-Related Air Pollution Metrics and SGA

Crude and adjusted odds ratios and 95% confidence intervals for traffic-related air pollution metrics and SGA are found in Table 4. In a model adjusted for maternal age, maternal race, marital status, maternal education, maternal smoking, parity and season of birth, there was an estimated eight percent decrease in odds of SGA for mothers living less than or equal to 50 m (Adjusted Odds Ratio (AOR) = 0.92, 95% Confidence Interval (CI) = 0.72 – 1.17) from the nearest major roadway as compared to mothers living more than 300 m from the nearest major roadway. The odds of SGA were reduced four percent for every 1000 m a maternal residence was away from a major roadway (OR = 0.96, 95% CI = 0.94 – 0.97). After adjusting for maternal race, education, age, maternal smoking, marital status, parity, and season of birth, similar results were observed but they were no longer statistically significant (AOR = 0.98, 95% CI = 0.96 – 1.00). There was a positive, but non-significant association with SGA and the highest category of DWTD (OR = 1.03, 95% CI = 0.90 – 1.17). After adjusting for covariates, the association between SGA and the highest category of DWTD was negative and non-significant (AOR = 0.96, 95% CI = 0.84 – 1.09) (Table 4). The results suggest that there are no significant associations between maternal residence distance from a major roadway and SGA in Harris County.

Discussion

This study examined the association between distance from maternal residence to a major roadway and SGA as well as DWTD and SGA in infants born in Harris County, Texas in 2006. It is the first to look at the associations between these traffic-related metrics and SGA in the United States. There were no significant associations found between traffic-

related air pollution and SGA in this study population after controlling for maternal factors and season of birth.

Few studies have evaluated associations between traffic-related air pollution and SGA. Brauer et al. conducted a study in Vancouver, British Columbia, Canada and reported a 26 percent increase in the odds of SGA for mothers who live less than 50 m from a highway (AOR = 1.26, 95% CI = 1.07 – 1.49) [10]. Other measures of road proximity (< 150 m from highway or major roadway) showed no significant associations with SGA in the Brauer et al. study. The adjusted odds ratio for maternal residences 50 m or less from major roadways showed a negative, non-significant association in the present study. Another Canadian study from Montreal found no significant association for those mothers living less than 200 m from a highway and SGA in crude (OR= 1.08, 95% CI = 0.98 – 1.19) and adjusted models (AOR = 1.06, 95% CI = 0.96 – 1.17) [11]. The present study found a positive association for maternal residences that were 101 – 200 m from a major roadway, but it was not statistically significant. A Dutch study conducted in Rotterdam found positive, but non-significant associations at the highest quartile of DWTD (over 1.2 million vehicles/24 hours*m) and proximity to roadways (< 50 m) and SGA (AOR = 1.12, 95% CI = 0.78 – 1.59; AOR = 1.14, 95% CI = 0.77 – 1.68, respectively) [12].

The distance on average from geocoded maternal residence to a major roadway was 1650 m for this study. The distance to major highways was more than 228.6 m, 750 ft, for approximately 95% of subjects in this present study so the DWTD metric was calculated as 0 for most of the study population. There are studies that have used the DWTD metric looking at adverse birth outcomes in California. A study conducted by Von Behren et al. found 38%

of subjects did not have a major roadway within 152 m (498.7 ft) from their birth residence in the San Francisco Bay Area [18]. The population density per square mile of land area for the San Francisco – Oakland-Fremont area is 1754.8 persons per square mile while the Houston-Sugarland-Baytown Metro area has a population density of 673.7 persons per square mile [15]. This difference could partially explain the greater proportion of mothers with DWTD values in the San Francisco Bay Area as compared to Houston. Approximately twenty percent of the subjects in the Wilhelm and Ritz study were in the lowest quartile of exposure for DWTD as compared to 95% in the present study [16]. When looking at population density at a county level, Los Angeles County and Harris County have approximately the same amount of people per area, 2419.6 persons per square mile and 2402.4 persons per square mile, respectively [19,20]. However, Los Angeles County has more miles of major roadways than Harris County [21,22]. An explanation of why more maternal residences were captured for the DWTD metric in the Wilhelm and Ritz study could be due to an increased number of major roadways in the maternal residence buffer.

A possible limitation of this research is exposure misclassification related to mapping the geocoded maternal residence at birth. The assumption was that mothers did not move during pregnancy. It is expected that this would introduce nondifferential misclassification. There was no information on maternal residential mobility for this study, but a previous study found that maternal residential mobility did not affect exposure assessment in Texas [23]. Next, the date of last menstrual period (LMP) was taken from the birth certificate to calculate gestational age. Although using LMP is the one true way to calculate gestation, it is riddled with biases such as recall error from mothers. This could lead to misclassification of

the SGA outcome. The clinical estimate of gestational age may also lead to outcome misclassification because the procedure to measure infants is not standardized [24]. Though the exposure assessment for this study is similar to others, the outcome definition may explain the difference in the magnitude of associations. Only full-term singleton infants were included in these analyses. Stronger associations between ambient air pollution such as polycyclic organic matter (POM) and pre-term SGA infants have been found in the literature [25]. Future investigations should consider exploring term SGA, pre-term SGA, as well as pre-term births as three distinct outcomes. This study did not have information on indoor exposures (e.g. environmental tobacco smoke, emissions from gas stoves or heaters, and attached garages), and occupational or commuting sources of exposure. It was assumed using these exposure metrics that pregnant women spent their time at home and that the outdoor air infiltrated it.

There are strengths of this study. First, the large number of study subjects, 52,257, gives this study statistical power. Few studies have employed study sizes as large as this study population. There is one prospective cohort study that had close to 100,000 births [11], one study looking at DWTD and low birth weight had a similar number of births with 50,933 [16]; and three other studies looking at DWTD and adverse birth outcomes such as spontaneous abortion, gestational diabetes, pregnancy induced hypertension, pre-eclampsia, birth weight, and SGA had less than 7500 subjects [12,26,27]. Another strength of this study was that the birth year and annual traffic counts used to calculate the DWTD metric were both obtained for the year 2006. Lastly, the use of geocoded maternal addresses allowed for a more accurate calculation of distance from residence to major roadway.

Conclusion

In conclusion, this study found no evidence of an association between distance from major roadways to maternal residence at delivery and SGA infants born in Harris County, Texas. As found during this study, DWTD must be used with care when population density of the geographic area of interest is low or there are few major roadways. This is the first study to use this exposure metric to determine if there is an association between traffic-related air pollutants and SGA in the southern United States.

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Table 1. Crude Odds Ratios (OR) and 95% Confidence Intervals (CI) for Associations between Demographic Characteristics and SGA Infants in Harris County, 2006 (n = 52,257)

Characteristics		Full-Term Singleton Infants (%) n = 52,257	SGA Term Infants (%) n = 5,289	Crude Odds Ratio (95% CI)
Infant Sex	Female	49.60	48.18	Reference
	Male	50.40	51.82	1.07 (1.01 – 1.13)
Maternal Race	Non-Hispanic White	32.37	27.96	Reference
	Other[a]	26.70	27.59	1.22 (1.13 – 1.32)
	Black	18.33	29.17	2.01 (1.86 – 2.16)
	Hispanic	22.59	15.28	0.77 (0.70 – 0.84)
Maternal Education	More than High School	39.31	33.11	Reference
	High School	23.55	26.28	1.37 (1.27 – 1.47)
	Less than High School	37.06	40.48	1.33 (1.25 – 1.42)
Maternal Smoking	Non Smoker	95.24	92.91	Reference
	Smoked Prior, Stopped Early	1.76	1.70	0.99 (0.74 – 1.23)
	Smoked Through Pregnancy	2.05	4.01	2.25 (1.93 – 2.63)
Maternal Age	20 - 24 years	26.47	29.72	Reference
	≤ 19 years	12.57	18.11	1.33 (1.22 – 1.45)
	25 - 34 years	48.80	42.71	0.76 (0.71 – 0.81)
	≥ 35 years	12.16	9.43	0.67 (0.60 – 0.74)
Parity	1 or more	61.70	51.69	Reference
	Nulliparous	38.26	48.25	1.58 (1.49 – 1.67)
Marital Status	Married	57.99	47.19	Reference
	Not Married	42.01	52.81	1.62 (1.53 – 1.72)
Season of Birth	Warm (Apr - Sep)	49.95	49.61	Reference
	Cool (Oct - Mar)	50.05	50.39	1.01 (0.96 – 1.08)

[a] Other includes American Indian, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Samoan, Other Pacific Islander, and Other

Table 2. Mean, Median, Range and Percentile Distributions for Distance (m) from Geocoded Maternal Residences to Nearest Major Roadway and DWTD (vehicles/24 hour * m) (n = 52,257)

	Distance (m)	DWTD (vehicles/24 hour*m)
Mean	1,650.93	1,966.52
Standard Deviation	1,535.82	15,802.31
Minimum	6.52	0.00
5^{th} percentile	183.91	0.00
25th percentile	614.37	0.00
Median	1,194.71	0.00
75th percentile	2,237.20	0.00
95^{th} percentile	4,550.33	392.53
Maximum	18,903.45	270,605.80

Table 3. Distribution of SGA Cases and Non-Cases by Distance (m) from Geocoded Maternal Residence to Nearest Major Roadways (n = 52,257)

Distance (m)	Cases		Non-Cases	
	No.	Percent	No.	Percent
> 300	4,761	90.02	42,319	90.10
201 - 300	216	4.08	1989	4.23
101 - 200	190	3.59	1549	3.30
51 - 100	44	0.83	425	0.90
0 - 50	78	1.47	686	1.46

Table 4. Crude and Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Associations between Traffic-Related Air Pollution Metrics and SGA in Harris County, Texas, (n = 52,257)

Traffic-Related Air Pollution Metric	OR (95% CI)	AOR [a] (95% CI)
Distance (m) to Major Roadway		
> 300	Reference	Reference
201 - 300	0.97 (0.84 – 1.11)	0.94 (0.81 – 1.08)
101 - 200	1.09 (0.94 – 1.27)	1.05 (0.90 – 1.22)
51 - 100	0.92 (0.67 – 1.26)	0.87 (0.63 – 1.19)
0 - 50	1.01 (0.80 – 1.28)	0.92 (0.72 – 1.17)
Distance (m) to Major Roadway[b]	0.96 (0.94 – 0.97)	0.98 (0.96 – 1.00)
DWTD[c]		
< 95th Percentile	Reference	Reference
≥ 95th Percentile	1.03 (0.90 – 1.17)	0.96 (0.84 – 1.09)

[a] adjusted for maternal age, maternal race, maternal education, maternal smoking status, marital status, parity, and season of birth

[b] per 1000 m

CHAPTER V: CONCLUSION

This project used three different exposure metrics: (1) U.S. EPA NATA data, (2) air monitoring data, and (3) distance from maternal residence to major roadway to determine the association between SGA and combustion pollutants in the Southern United States. Others have used similar exposure metrics and have found positive associations between air pollution and other adverse birth outcomes. We found no associations between air pollution and SGA; however, the results contribute to the growing body of literature assessing maternal exposure to ambient air pollution and adverse birth outcomes.

This project has many strengths. The first is the sample size for each aim's study population. Each aim had study population sizes much larger than others using similar exposure metrics. Next, using birth certificate data allowed us to control for many potential confounders i.e. maternal smoking. Limitations to this study included the assumption that the ambient air toxic levels obtained from census tract data and air monitoring data are similar to the personal exposure levels. Many factors contribute to personal exposure to PAHs and other air toxics, such as dietary exposures to PAHs and air conditioning usage, and were not included in the exposure metrics.

Recommendations for future work should consider the results from three different outcomes: term SGA, preterm SGA, and all SGA. Many studies in the literature were not explicit with regard to which outcome was explored. Next multi-pollutant models, particularly those with particulate matter and PAHs, should be completed because the population is exposed to a mixture of air toxics in the ambient air.

Overall, this project was the first to look at SGA and combustion pollutants in the Southern United States with three different exposure metrics: (1) U.S. EPA NATA data, (2) air monitoring data, and (3) distance from maternal residence to major roadway. Although there was no evidence of associations found between SGA and the air pollutants mentioned in these studies, the results contribute to the body of literature assessing maternal exposure to ambient air pollution and adverse birth outcomes.

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