ENVIRONMENTAL TOXICANTS AND PRETERM BIRTH IN MEXICO CITY: A GEO-SPATIAL APPROACH FOR USE IN EPIDEMIOLOGY

by

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DEDICATION

During this long journey, there have been many people that have inspired, supported, and pushed me to new levels that I never thought possible. Simply put, they are just too many to mention. This work is dedicated to them, but especially to my parents and family members whose time I stole and hope to remake, and to my love that has made me a better person.

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CHAPTER I

INTRODUCTION

Preterm Birth

In 2004, 12.5 percent of births in the United States were preterm, that is, born with less than 37 weeks of gestation (IOM 2007). Preterm birth and its effects constitute a major health problem in the United States as well as in other parts of the world, especially developing countries. It is known as one of the main contributors to the rising rates on infant mortality in the United States, as well as in developing countries (Ngoc, Merialdi et al. 2006). It has been estimated that the economical burden on society reaches $26 billion per year, which translates to about $51,600 per infant (IOM 2007).

Preterm birth is caused by many factors which may include individual level behavioral and psychosocial factors, neighborhood characteristics, environmental exposures, medical conditions, infertility treatment, biological factors, and genetics (IOM 2007).

Preterm birth can impact both children and adults. The United Nations Millennium Developmental Goals (UN-MDGs) include the mission to reduce by two thirds, between 1990 and 2015, the under-five mortality rate (UN 2010). Not only does

this rate measure infant mortality due to preterm birth, but it indicates the level of child health and developmental resources of a country.

Infants born preterm have a higher risk of mortality and health complications compared to infants born at term. In addition, perinatal outcomes are important markers of future child and adult health. It is also important to recognize the impact that a preterm baby has on families that must deal with the emotional and economical distress.

Air Pollution and Preterm Birth

Air pollution has a variety of natural and anthropological sources which include industrial emissions, motor vehicles, wood burning, and fugitive dust. Criteria air pollutants are some of the most common pollutants regulated by regulatory agencies using environmental and human health-based criteria. They include particle pollution, also called particulate matter (PM), carbon monoxide (CO), ground-level ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and lead (Pb). As the use of lead has been phased out of many countries, including the study location proposed in this research, discussion and analysis will be primarily devoted to the "major" criteria pollutants, but I will briefly discuss the effects that lead and its cumulative exposure has on preterm birth since aim 3 addresses this theme.

Air pollution has an enormous variety of effects on the health of individuals (Curtis, Rea et al. 2006). The following paragraphs will discuss the influence that has been found through epidemiological studies about air pollutants and their health effects related to perinatal health (i.e. preterm birth). For the ease of understanding the

effects of individual pollutants, research results will be discussed under each air pollutant type.

Particulate Matter (PM)

Particulate matter comprises the most visible and obvious form of air pollution which could be liquid or solid. Particulate matter may be organic or inorganic and is commonly suspended in the air near sites of pollutant emissions such as industries, highways, or power plants. The different sources of particulate matter would differ in the size of particles that they form, something very relevant to health.

Toxic effects produced by particulate matter depend on their size, measured by aero-dynamic diameter, with particles less than 10μm (PM_{10}) or 2.5 μm ($PM_{2.5}$) in aerodynamic diameter being categorized hazardous since they can easily be inhaled and reach the alveoli where gas-exchange processes occur. Different studies have examined the comparability of exposure measurement method and the characterization of particulate matter (Cicero-Fernandez, Torres et al. 2001; O'Neill, Loomis et al. 2004; Pearce, Rathbun et al. 2009). Other researchers have studied the relationship that particulate matter (PM_{10}, $PM_{2.5}$, or Total Suspended Particles (TSP)) has to mortality and morbidity associated with cardiovascular and respiratory health outcomes (Pope, Burnett et al. 2002; Künzli, Jerrett et al. 2005; Huynh, Woodruff et al. 2006). By contrast, relatively few studies have evaluated the relationship that particulate matter has with perinatal outcomes. Huynh et al. (2006) found $PM_{2.5}$ exposure to be associated with a small effect on preterm birth after adjusting for maternal age, maternal race/ethnicity, maternal education, marital status and parity. First trimester exposures, as well as the last two weeks of pregnancy, are important critical windows

of exposure found in this study. There was no association between TSP exposure and low birth weight and prematurity. Another study found an association during the last 6 weeks before birth with exposure to PM_{10} (Sagiv, Mendola et al. 2005).

Other studies have reviewed the existing literature on particulate matter and preterm birth and have concluded the need for further research that would incorporate better exposure estimates based on plausible biological mechanisms, toxicological assessment, and identify vulnerable windows of susceptibility (Glinianaia, Rankin et al. 2004; Maisonet, Correa et al. 2004; Sram, Binkova et al. 2005; Slama, Darrow et al. 2008)

Ozone (O_3)

An important molecule that plays a vital role in the stratosphere by filtering and blocking harmful ultraviolet light, ozone has, in contrast, an adverse effect when exposure occurs at the tropospheric level. Ozone is a highly reactive gas and is a component of photochemical smog. Ozone is formed from nitrogen oxides (NO_x), reactive hydrocarbons and sunlight. Thus, warmer and sunnier seasons will tend to produce higher levels of this contaminant. Exposure to high concentrations of this air pollutant results in severe irritation and headaches. It irritates the eyes, upper respiratory system, and lungs. Once this reacts with the human body, the synthesis and production of free radicals or reactive oxygen species occurs. These species can cause lipid peroxidation, oxidation of sulfhydryl groups (-SH), and relevant oxidative damage (Manahan 2005).

Studies that have looked at the relationship between ground-level ozone exposure and preterm birth have been largely inconclusive, but recent published data

have shown that there is a small association between exposure to ozone and preterm birth (Salam, Millstein et al. 2005; Davis, O'Neill et al. 2008). The inconclusive findings may in part be due to the high spatial variability that ozone exhibits in outdoor air, resulting in a greater degree of exposure measurement error and bias toward the null in epidemiologic analyses.

Carbon Monoxide (CO)

A common cause of accidental poisoning, CO has other effects especially in the respiratory and cardiovascular systems. Exposure to CO will cause the gas to enter the blood through the alveoli. There it will react with the hemoglobin transporter and converts to oxyhemoglobin (O_2Hb) to carboxyhemoglobin (COHb). COHb prevents oxygen from being carried out to body tissues where it is needed for aerobic cellular processes.

In one study, CO exposure, at any time during pregnancy, was not related to preterm delivery (Huynh, Woodruff et al. 2006). In another study, preterm birth was associated with exposure to CO during the last month of pregnancy (odds ratio (OR) of 1.08, 95% CI, (1.01-1.15)), for a 1.0 ppm increase in concentration (Liu, Krewski et al. 2003).

.**Sulfur Dioxide (SO_2) and Nitrogen Dioxide (NO_2)**

Sulfur dioxide is produced by the burning of coal, vehicle and refinery emissions, and oil refineries. It is an irritant of the eyes, skin, mucous membranes, and respiratory tract. It is also a major precursor to acid rain, as the SO_2 when mixed with water forms sulfurous acids, hydrogen sulfite ions, and sulfite ion. A study conducted in the Czech Republic reported that low birth weight and prematurity were associated

with SO_2 exposure (Bobak 2000). Liu et al. (2003) found an association between preterm birth and exposure to SO_2 (OR- 1.11, 95% CI (1.01-1.22) for a 5ppb increase) during the last month of pregnancy. Time series analysis performed by Liu et al. (2005) showed an association of preterm birth onset with exposure to SO_2 during 6 weeks before birth.

On the other hand, nitrogen dioxide is produced largely by industrial/vehicle combustion. It can also be formed in the atmosphere through photochemical processes that would cleave and produce different species of nitrogen oxides (NO_x). A Korean study that used spatial and temporal modeling for estimating exposure and a birth cohort consisting of 52,113 singleton births found an association between exposure to NO_2 during the first trimester and preterm birth (OR- 1.24) (Leem, Kaplan et al. 2006).

Lead and Preterm Birth

Researchers have concluded that the available epidemiologic data to date supports an adverse relationship between lead exposure and preterm birth (IOM 2007). Most developed countries and some developing countries have reduced the environmental sources of lead exposure of their populations. In Mexico City this process began when government started to phase out lead in gasoline in 1991, prior to recruitment of the cohorts evaluated in this study.

Research has shown that internal stores of lead could potentially be important biomarkers of cumulative exposure to lead, as well as serve as an important predictor of perinatal outcomes (Gonzalez-Cossio, Peterson et al. 1997; Gomaa, Hu et al. 2002; Hu, Shih et al. 2007). Several studies have concluded that an adverse association

existed between high lead exposure and prematurity (Andrews, Savitz et al. 1994; Ettinger, Lamadrid-Figueroa et al. 2008; Cantonwine, Hu et al. 2010), Several studies have estimated the acute exposure of lead by measures in whole blood (plasma or whole blood, cord blood) (Torres-Sanchez, Berkowitz et al. 1999; Lamadrid-Figueroa, Tellez-Rojo et al. 2007). Researchers have estimated a greater (threefold) risk for preterm birth (1.2-7.4 95%CI) for women with blood lead levels greater than 10µg/dL (Andrews, Savitz et al. 1994).

Chuang et al. (2001) have demonstrated that maternal blood lead is correlated to umbilical cord blood lead, thus serving as a valid predictor of fetal exposure. More recently, plasma lead has been shown to be a better measure of the amount of lead that is biologically available. Blood lead is a measure of the amount of lead in blood and plasma. Nonetheless, plasma lead accounts for about 3% of the total blood lead concentration and is thought of as the portion that is able to reach and cross the placenta causing harm to the fetus (Figure 1).

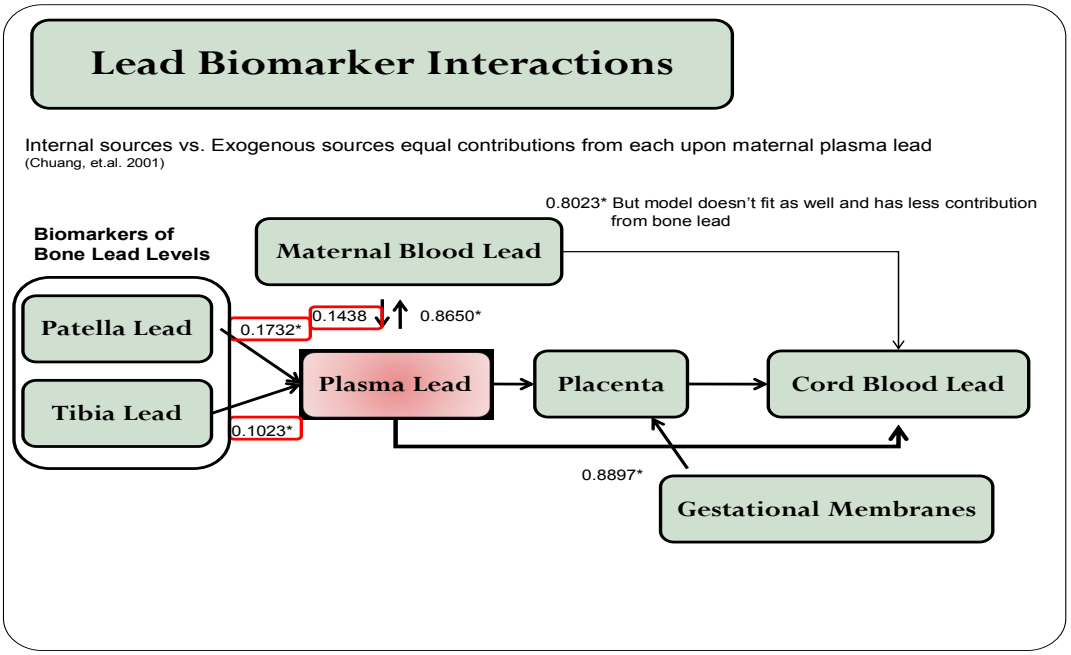

Figure I-1. Lead Exposure Biomarkers: Exogenous vs. Endogenous. (Chuang et al., 2001).

Air Pollution Exposure Assessment

Much of the research pertaining to air pollution and perinatal outcomes is based on data sets that have been formed by combining data from birth registries and air pollution data obtained from outdoor air quality monitors. Because of the spatial variability of pollution within a geographic region that may not be captured when measured data from monitors is averaged, there has been a growing interest in creating spatial and temporal models that go beyond that averaging approach to predict exposure estimates for people without having to obtain personal exposure monitoring data.

Development of models to assess intraurban air pollution exposures is especially useful for assessing impact to health. Several ways to characterize air pollution exposures exist (Jerrett, Arain et al. 2004). In some cases, area-level average air pollution (e.g. city wide average) may be sufficient to represent individual

exposures. Other methods require modeling at a higher resolution due to the high spatial and temporal variability that certain air pollutants may show.

In many cases exposures are expected to decline with distance from source due to mixing and dilution effects. Distance can then be used as a proxy of exposure in order to examine differences between exposed and unexposed groups where no other sources of direct measures of exposure are available. This represents the most basic approach in differentiating air pollution exposures. Janssen et al. (2001) found a significant positive association between pollution concentration and decreasing distances of schools from major automotive routes. In another study, exposure was estimated using a traffic inventory which determined the amount of cars passing by per hour, matched to residence location (Wyler, Braun-Fahrländer et al. 2000).

Gradually, geographical information systems (GIS) have gained a wide acceptance in the field of epidemiology and public health. GIS are useful tools for visualizing and exploring health outcomes and their relationship to geo-coded data, as well as for enhancing exposure assessments and modeling of disease clusters. Air pollution exposure has been modeled through the use of interpolation models, including kriging derived from geographical information systems (GIS) (Briggs, Collins et al. 1997; Leem, Kaplan et al. 2006; Kim, Sheppard et al. 2009).

The study of geo-statistics deals with different techniques that help us understand and model spatial variability through prediction and simulation. It has as a primary goal to estimate the spatial relationships between sample values. This estimate is then used to predict unobserved values and provide an estimate of the variance of the predicted error.

Kriging is an interpolation technique used for predicting values at unsampled locations based on concentrations sampled spatially. It has been used for estimating air pollutant concentrations in ambient air and for mapping gradients in urban air quality (Briggs, Collins et al. 1997; Leem, Kaplan et al. 2006; Liao, Peuquet et al. 2006; Shad, Mesgari et al. 2009).

One assumption is that kriging will improve the accuracy and robustness of the air pollution exposure estimates since it involves smoothing (interpolating) between monitors and is a more refined approach than simply assigning the exposure from the nearest monitor or assigning a citywide average. However, whether estimates of the effect of air pollution exposure on preterm birth differ substantially using kriging versus alternative exposure assessment approaches is of interest for interpreting and comparing studies, since not all published research has had available information on the mother's residential location.

Potential Mechanisms for Air Pollution's Association with Preterm Birth

Although the causes of preterm birth are multiple, there are just a few routes hypothesized to lead to preterm birth (Figure I-2). Important common pathways include stress, systemic or maternal genital tract infections, placental ischemia or vascular lesions, and uterine overdistension. These factors are not completely understood, but it is known they produce uterine contractions and lead to birth.

Several hypotheses about the mechanism that triggers the development of preterm deliveries have been offered. Gravett et al. (1994) have shown evidence to suggest that infection provokes preterm births in monkeys whose amniotic fluid was injected into the amniotic fluid with group B streptococci. Infection prior to delivery

can trigger intrauterine inflammation which helps stimulate preterm labor. Moreover, other groups of researchers have speculated other pathways that involve: the periodontal status of the mother, which may trigger inflammatory mediators in the intrauterine environment; smoking status, which may influence the inflammatory pathway; and inflammation, which can lead to placental function deterioration and ultimately to preterm delivery (Petruzzelli, Celi et al. 1998; Klesges, Johnson et al. 2001; Mcgaw 2002).

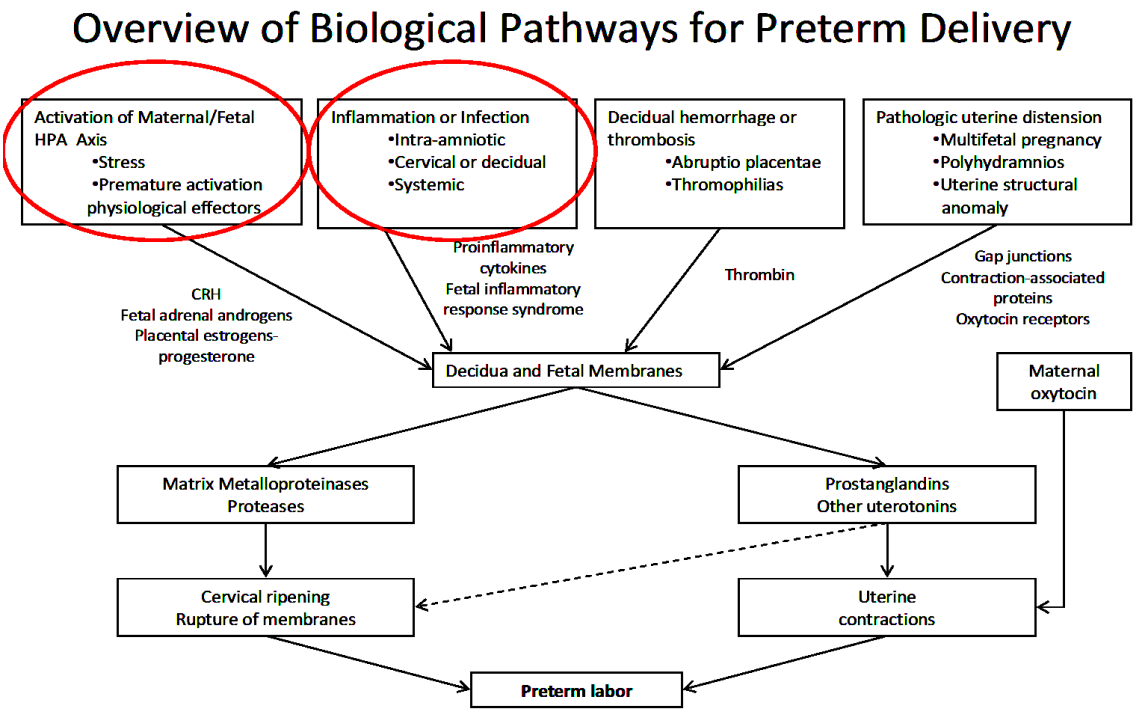

Figure I-2. Biological Pathways for Preterm Birth. (IOM, 2007. p.178).

Dissertation Overview

This dissertation is composed of five chapters: the introduction (this chapter), three main chapters, and chapter five that summarizes the conclusion from the findings of the three main chapters. The overall aim of the dissertation is to develop and compare air pollution exposure metrics, and then link these metrics to geo-referenced women from the ELEMENT (Early Life Exposure in Mexico to Environmental Toxicants) mother-infant cohort in Mexico City for the purpose of evaluating environmental contributions to preterm birth risk. Overall, findings from this dissertation will be pertinent to air pollution exposure assessment methods that could be used to estimate individual exposure in an ongoing Mexican birth cohort titled: Air Pollution and Preterm Birth in Mexico City: A Mechanistic Study in Mexico City.

Recent interest in, and the rise of prematurity rates has sparked new scientific research that aims to recognize possible risk factors. This research has helped to reiterate to governmental entities and the scientific community the importance of identifying and learning more about how environmental toxicants may influence preterm birth. Because of this interest, the Institute of Medicine (IOM) convened a committee, the Committee on Understanding Premature Birth and Assuring Healthy Outcomes, to assess the current state of the science on the causes and consequences of preterm birth. Similarly, researchers from around the world convened at a workshop in Mexico City (September, 2007) to identify differences in methodologies used among previous epidemiological studies of air pollution and perinatal outcomes. Four priority areas of interest for further research were agreed upon: (1) confounding and effect modification, (2) spatial and temporal exposure variations, (3) vulnerable windows of exposure and (4) multi-pollutant exposures (Woodruff, Parker et al. 2009).

The proposed dissertation will deal in part with some areas of interest found from these workshops, and thus will help to improve the state of knowledge on the subject of exposure assessment methods used in environmental epidemiology, preterm birth and air pollution's influence, and possible interaction with biomarkers of lead exposure that may modify any associations discovered in susceptible populations such as pregnant women.

In Chapter 2, four air pollution exposure assessment methods (spatial averaging, nearest monitor, inverse distance weighting, and ordinary kriging) to estimate daily air pollution concentrations are developed and compared for the pollutants PM_{10}, $PM_{2.5}$, O_3, CO, NO_2, and SO_2 concentrations on an hourly basis. From this database, the four methods were constructed and evaluated for their performance in air pollution estimation.

Using exposure assessment methods to estimate daily air pollution concentrations developed in Chapter 2, we will construct PM_{10} and O_3 individual metrics for different windows in pregnancy (first, second, and third trimester averages, and entire pregnancy period). Chapter 3 assesses the differences between air pollution exposure assessment methods and how estimated metrics influence preterm risk effect estimates in Mexican women recruited in different hospital of Mexico City from 1994 to 2004. This analysis benefits from existing socio-demographics data and covariates of interest that could confound the association between air pollution and preterm birth. Recent workshops, as well as inconsistent and inconclusive findings relating air pollution and preterm birth motivate this study. With especially high levels of air

pollution, Mexico City is a particularly useful site for this study to add to the already existing scientific literature.

Using the methods and analysis performed in Chapter 3, we will examine in Chapter 4 the effect-measure modification that chronic lead exposure (measured in bone: tibia and patella) has on the association of air pollution with preterm birth. The advantage of having measured environmental exposures and biomarkers (air pollution and lead) in the Mexican birth cohort facilitates asking questions that are hard to investigate in other settings. This is the only study, to our knowledge, that seeks to determine if effect-measure modification is present when pregnant women with high and low bone lead exposure are exposed to air pollutants during relevant windows of exposure in pregnancy.

Lastly, Chapter 5 will serve as a summary of the major findings in the main chapters of this dissertation. Also, it will serve as a place to discuss future directions and ideas that will help improve future studies pertaining to air pollution and reproductive outcomes.

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CHAPTER II

AIR POLLUTANT EXPOSURE METRICS FOR PERINATAL EPIDEMIOLOGY IN MEXICO CITY, MEXICO

INTRODUCTION

High levels of air contaminants are encountered in major urban areas of developing countries where a large population of individuals is exposed, thus making air pollution a major public health issue. A growing number of urban residents in developing countries are living in areas with levels of air pollution that exceed the World Health Organization (WHO) air quality guidelines (Cohen, Ross Anderson et al. 2005).

Previous studies on air pollution health risks have found associations between air pollution and mortality/morbidity (Borja-Aburto, Loomis et al. 1997; Brunekreef and Holgate 2002), cardiovascular disease (Künzli, Jerrett et al. 2005; Park, O'Neill et al. 2008), and adverse pregnancy outcomes (e.g. low birth weight, preterm birth, intrauterine growth retardation, and fetal health) (Glinianaia, Rankin et al. 2004; Sram, Binkova et al. 2005; IOM 2007; Slama, Darrow et al. 2008; Woodruff, Parker et al. 2009). Many of these studies have examined commonly monitored air pollutants: (ozone (O_3), particulate matter less than 10 and 2.5 micrometer in aerodynamic

diameter (PM_{10} and $PM_{2.5}$), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2)).

Several publications on outdoor air pollution and perinatal outcomes have relied on birth registry datasets to assess birth outcomes and air pollution data obtained from government-run air quality monitors to create estimates of personal exposure to these contaminants (Sagiv, Mendola et al. 2005; Bell, Ebisu et al. 2007; Chang, Reich et al. 2012). For the ultimate goal of estimating daily air pollution exposure at the individual level, several exposure assessment methods have been developed (Jerrett, Arain et al. 2004). Some studies have had the ability to use exposure assessment methods that account for the mother's residential location (Nethery, Leckie et al. 2008), proximity to traffic or other sources of emission (Wilhelm and Ritz 2003; Yorifuji, Naruse et al. 2011), land-use regression models (Slama, Morgenstern et al. 2007; Brauer, Lencar et al. 2008), and even personal monitoring of mother's during pregnancy (Jedrychowski, Galas et al. 2005; Perera, Tang et al. 2005; Perera, Li et al. 2009) to assess individual air pollution exposure. Other models have also been explored to reduce exposure measurement error, due to the high spatial and temporal variability that certain air pollutants may show (Zou, Wilson et al. 2009).

In some cases, area-level or spatial averaging of air pollution (e.g. city-wide averaging) may be sufficient to represent individual exposures, especially for more spatially homogeneous pollutants and depending on the nature of the exposure (acute versus chronic) and/or health outcome under study. Previous studies have used spatial averaging to determine personal exposure to outdoor pollution (Brunekreef and Holgate 2002).

In many cases exposures are expected to decline with distance from a pollution source, such as a roadways or industrial facilities, due to mixing and dilution effects. Nearest monitor, inverse distance weighting, and ordinary kriging are methods that use distance to estimate exposure to outdoor air pollution in urban settings. If the location where the study participants lives or spends time is known, proximity to air pollution monitors, pollution sources, or features of land cover (e.g., buildings and vegetation) expected to reduce pollution concentrations can be used to enhance personal exposure models. Examples from epidemiologic studies that incorporated distance into their air pollution exposure metrics include: distance from schools from major automotive routes (Janssen, van Vliet et al. 2001), distance of mother's residence from highways (Brauer, Lencar et al. 2008), and number of vehicles passing by per hour matched to residential location (Wyler, Braun-Fahrländer et al. 2000).

Other approaches for estimating exposure to air pollutants interpolate between points of known concentrations to create a continuous spatial surface, so that any given geographic location can be assigned a unique concentration. Kriging is an interpolation technique used for estimating values at unsampled locations based on concentrations sampled spatially (e.g. a network of monitors sited around an urban area) (Jerrett, Burnett et al. 2005). More specifically, kriging models the spatial dependence, or spatial autocorrelation, of the values measured at sampled locations to construct the prediction for the unsampled locations. It has been used for estimating air pollutant concentrations in ambient air; assigning exposures when participant locations are unknown, and for mapping gradients in urban air quality (Lefohn, Knudsen et al. 1988; Briggs, Collins et al. 1997; Jerrett, Burnett et al. 2005; Leem, Kaplan et al.

2006; Liao, Peuquet et al. 2006; Iñiguez, Ballester et al. 2009; Shad, Mesgari et al. 2009).

One advantage of kriging is that it also allows calculation of uncertainty in the estimated values. However, kriging works best when a dense network of outdoor air monitors is available to capture spatial variability. Less dense networks will produce estimates with higher levels of uncertainty.

In epidemiological studies, it is essential to quantify the potential bias caused by air pollution exposure misclassification (Marshall, Nethery et al. 2008; Gryparis, Paciorek et al. 2009; Woodruff, Parker et al. 2009). No published studies to date have implemented interpolation methods to estimate individual exposure to air pollutants in Mexico City. This method has the potential to reduce bias resulting from exposure misclassification, especially in a population with the high levels of exposure to air contaminants that exist in Mexico City. This paper uses 2008 daily air pollution data from metropolitan Mexico City to construct and compare different methods for exposure assessment for application in future perinatal epidemiology studies where mothers' residential location is known. The metrics to be compared include citywide average (CWA), nearest monitor (NM), inverse distance weighting (IDW), and ordinary kriging (OK). The differences among these metrics will be evaluated in a simulated population from various regions of metropolitan Mexico City. Exposure metrics produced from these methods will be used to assess the relationship that air pollution has with preterm birth in a mother-infant pair cohort recruited from (1994-2005) in three hospitals and also for a future ongoing birth cohort in Mexico City.

METHODS:

Study Location

Mexico City's metropolitan area has an estimated population of 19 million (Brinkhoff 2006) and is located in a valley surrounded by mountain ranges that reach elevations of 2,240 meters above sea level. The metropolitan area is impacted by a diverse range of pollution sources that range from industrial refineries, to traffic emissions, to wind-blown dust from a dry lake basin. Traffic emissions are one of the principal sources of pollutants since nearly 3.5 million cars circulate in the metropolitan area (Secretaría del Medio Ambiente 2006). Although the metropolitan area often meets daily standards for six regulated 'criteria' pollutants (CO, PM_{10}, $PM_{2.5,}$ O_3, SO_2, and NO_2), it does not meet the annual standards (TableS-4) which regulate chronic exposure, with concentrations being almost double the levels for many pollutants. Consequently, Mexico City has notably high levels of PM_{10} and $PM_{2.5,}$ and O_3 and standards are not met in certain geographical locations in the city (Zuk, Tzintzun Cervantes et al. 2007).

Air Pollution Data

The air quality monitoring network in Mexico City ("Sistema de Monitoreo Atmosférico"), or SIMAT by its acronym in Spanish) provides data on the six criteria pollutants. The network consists of 36 stations that measure different pollutants throughout the metropolitan area. Of these 36 sites, 22 sample for ozone; 26 for SO_2; 18 for NO_2; 18 for CO; 14 for PM_{10}, and 9 for $PM_{2.5}$ (Zuk, Tzintzun Cervantes et al. 2007). The geo-referenced locations of these monitors and the pollutants they measure are shown in Figure II-1 and Table II-S5, respectively.

Data on these six air pollutants are publicly available at the SIMAT website (http://www.sma.df.gob.mx) maintained by the Mexico City government. We downloaded the data on December 9, 2009 for the whole calendar year of 2008. Prior to posting on the website, SIMAT staff cleaned and validated the data (Zuk, Tzintzun Cervantes et al. 2007; Retama-Hernandez 2011). PM_{10} and $PM_{2.5}$ were reported in mass units of micrograms per cubic meter ($\mu g/m^3$), whereas O_3, CO, NO_2, and SO_2 were reported in parts-per-million (ppm) in the downloaded data. O_3, NO_2, and SO_2 data were transformed from parts-per-million to parts-per-billion (ppb) to facilitate comparison of concentration levels with Mexico City air pollution standards which are reported in the units which we transformed. PM_{10}, $PM_{2.5}$, and CO retained the original units reported by SIMAT. Although data are available hourly for most of the pollutants, we summarized data as daily concentrations (24 hour averages) of particulates (PM_{10} and $PM_{2.5}$), $S0_2$, and NO_2, the daily 8 hour maximum moving average for CO, and the daily 8 hour maximum for ozone, from all available monitoring stations. These concentration averaging times were chosen to match the health-based regulatory standards in effect in Mexico City (Zuk, Tzintzun Cervantes et al. 2007). If more than 25% of the hourly values in a given day were missing, the daily concentration was coded as 'missing'. Subsequently in this paper, we use short term 'daily value' or 'pollutant concentration' to refer to these summaries.

Simulated Population Location Data for Exposure Estimation

Our goal is to construct and compare exposure metrics and eventually assign them to participants in a pregnancy cohort we are currently enrolling in Mexico City. To evaluate these metrics, we simulated a population of 1,000 pregnant women whose

residential locations are distributed across the metropolitan area. To restrict the area of simulated residences to a zone within which we can perform kriging, we created a polygon that surrounds the perimeter of the entire air monitoring network using ArcGIS 9.3.1 (ESRI, Redlands, CA) (Figure II-1). Then, we mapped the location of five monitoring stations that are sampling particulate matter for toxicological and compositional evaluation and comparison with the epidemiologic pregnancy cohort study. Thiessen polygons were then created to subdivide the exterior polygon into five zones surrounding these toxicological monitoring stations (Figure II-1). The ArcGIS Hawth's tools extension was then used to generate 200 random locations according to population density within each of the five polygons , omitting areas known to be uninhabited or where the study population is less likely to live (e.g., parks, industrial, non-residential areas). Population density, derived from Mexico City's 2005 census data (http://www.inegi.org.mx/) was used to choose potential locations in which to simulate individuals. This simulation foreshadows our plans to achieve a geographic balance of participant residences during the pregnancy cohort recruitment throughout the whole air monitoring network. Because of this, we use 'women' as equivalent to the simulated locations.

Exposure Assessment Methods

Citywide Averaging (CWA)

City-wide or spatial averaging uses a simple average of a given pollutant across all monitors within an identified geographic region to estimate an individual's exposure. Although straightforward to calculate, concentration estimates will not

reflect gradients of concentration or variability that may be present for certain air pollutants across a geographic location.

Nearest Monitor (NM)

The NM method determines the closest monitor to the study participant's location, and assigns the pollutant concentration at the monitoring site as the estimate of personal exposure. In the present study, distance was determined as the shortest straight line from the air quality monitor and the simulated residential location of the participants using ArcGIS 9.3.1 Hawth's Tools (ESRI, Redlands, Ca). The NM method relied on the three closest neighboring monitors, in case the nearest monitor was missing data for any given day. In that scenario, the second or the third closest monitor would provide data for the estimate.

Inverse Distance Weighting (IDW)

IDW computes predicted concentrations at the individual's location as a function of the inverse of the distance between the participant's location and the concentration at a subset of monitors (Shepard 1968). The higher the value of the power of the function applied to the distance (for example, $1/\text{distance}^5$ versus $1/\text{distance}^2$) will emphasize the contribution of the nearest points to the location and will produce a less smooth surface of concentrations when applied to several points (locations) in a given area. In contrast lower power values will give more importance to further points, creating a more smooth surface. The default square mathematical power value was selected to give more influence to surrounding points, which results in a smoother surface. Pollution values at the monitoring sites are averaged, with monitors closer to the individual's location given greater weight in the calculation of

the estimate. For this study, at least five monitors closest to the residence location were used to calculate the IDW exposure estimates using a maximum of 12 monitors for each pollutant.

Ordinary Kriging (OK)

Several forms of kriging have been commonly used to estimate exposure to air pollutants (Wong, Yuan et al. 2004; Leem, Kaplan et al. 2006; Liao, Peuquet et al. 2006; Brauer, Lencar et al. 2008). Similar to IDW, OK calculates a weighted average of concentrations at the monitoring stations to predict given participant's exposure. However, OK employs a function of distance referred to as a variogram, which describes the degree of spatial dependence, to model the spatial autocorrelation and construct weights. A positive-definite model of the variogram is fitted to a plot of semivariance (a measure of deviation between pairs of sample points) and distance, calculated from observed data. OK assumes that the variogram model that described the spatial dependence is constant across the region being mapped. Weights on sample points are solved for each estimate location based on the variogram describing relationships between sampled and unsampled points, and the relationship between sampled points.

The output of the OK operation is a continuous surface of estimated pollution concentrations within a defined geographical area, which can be mapped to grid cells. At any given location or grid cell, the value of the surface (i.e., a predicted concentration for the location) can be estimated, along with its estimation variance (or error). The error will be lower for points closer to the actual monitors. One of the advantages of OK over other interpolation methods is that the weights assigned to the

data are computed in a way that minimizes the variance of the standard error, whereas IDW uses an assignment of weights that is not informed by the sampled data.

We expected that seasonal patterns in outdoor pollution variation in Mexico City, a relatively temperate climate, would fall into two categories, rainy (May through October) or dry season (November through April). The rainy and dry seasonal periods were used for calculating longer-term averages and comparing exposure metrics.

Statistical Analysis

Descriptive statistics for daily concentration in 2008 for each air pollutant were calculated, and Pearson correlation coefficients were calculated between pollutants. Additionally, for each pollutant, correlations were calculated daily across exposure assessment methods for each woman, both in the city as a whole and in five zones. The mean difference in exposure estimates for the 200 participants in each of the five Thiessen polygons or zones were also calculated to assess regional differences and method performance.

In light of the participant burden of acquiring individual-level exposure in perinatal studies, our working hypothesis is that using estimates of air pollution exposure produced by kriging can reflect spatial variability and provide an improved proxy of individual-level exposure superior to the other three methods. Thus, in subsequent comparisons we use the values and variances of the kriging estimates as the point of reference for comparing the performance of each method, in the absence of a true 'gold standard' (measured concentration at the location of the simulated participants' homes).

Variogram Modeling

The R package, gstat, contains a function that creates empirical and experimental variograms. Once the empirical variogram has been created, the variogram can be fitted by seeding initial parameter values for sill, model type, nugget, and range. Variogram models for this analysis did not include a nugget effect, so the parameter was not included in the model. Initial values were then seeded for each specific air pollutant. Sill and ranges selected were 170 and 12,000 for PM_{10}; 0.17 and 10,000 for O_3; 0.16 and 8,000 for CO; 0.04 and 4,500 for NO_2; and 0.40 and 12,000 for SO_2. The gstat package then fits the models using the optimal parameters selected by the weighted least square method from the seeded values. All models had a spherical fit.

Model Evaluation

We compare CWA, IDW, and NM methods to OK by computing the absolute value of the difference between each method and OK, and by comparing the variances of the estimated values from each method to the variance of the OK estimates.

Furthermore, as detailed below, we use cross-validation to assess the performance of interpolation methods. Cross validation, commonly referred to as the "leave-one-out" approach, where a sampling site (in this case, one of the monitoring stations measuring the pollutant of interest) is removed from the dataset one site at a time, and the remaining data are used to predict the pollutant concentration at that particular site. The root mean squared error (RMSE) produced from the daily cross validations of different covariance models were used to compare method performance and precision in terms of predicting the monitored concentration. An RMSE of zero is

indicative of prediction of the parameter of interest (air pollution concentration) with great accuracy, although such values are practically impossible to achieve.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(z_i - \hat{z_i})}$$

That is, RMSE compares the interpolation estimates in this paper $\hat{z_i}$ = the estimated pollutant concentration at location *i*; to z_i = the air pollutant concentration at location *i*. The number of pollutant-specific monitoring sites is *n*, which varies depending on the pollutant. The gstat package in R was used in cross validation analysis for IDW and OK results (Pebesma 2004).

Creating the Metrics

Daily exposure estimates for calendar year 2008 were constructed for each location using the above described exposure metrics. We produced descriptive statistics on the resulting outdoor pollution estimates, overall, by season, and by region. For the OK estimates, only those residences that fall within each pollutant-specific polygon can be assigned a concentration for a given pollutant, since outside these polygons, the method is essentially extrapolating and not interpolating, and standard errors are large.

Air pollution exposure metrics were calculated for each individual day using all four exposure assessment methods and then averaged in order to calculate seasonal averages and construct trimester windows during pregnancy.

The daily pollutant values at each monitoring site were converted into the CWA, NM, IDW, and OK metrics using ArcGIS (ESRI, Redlands, Ca.), Statistical Analysis System (SAS version 9.2; SAS Institute, Inc. Cary, NC) and R, Version

2.11.0, package 'gstat'. Because the CWA does not account for spatial variability, a single CWA was applied to all 1,000 women on each day. In contrast, up to 36 different values (maximum number of monitors) of a given pollutant on a given date were assigned to the women according to the nearest monitor method; i.e., locations close to a given monitor received the same value as the monitor. A unique inverse distance weighted estimate for each woman was predicted depending on her residence location. Ordinary kriging was calculated using the gstat R package (Pebesma 2004) and the R 2.7.2 software (Team 2011)

First, we assessed the data distribution by exploring histograms and quantile-quantile plots. OK variogram parameters are affected by positive skewness in the air pollution data, so air pollution data were log-transformed to facilitate variogram parameter estimation. OK requires that variogram parameters (sill, nugget, range) be determined prior to obtaining the spatial surface of predicted air pollution concentrations. Thus, we examined three different models (Gaussian, exponential, and spherical), which assume different distributions of the input data and examined variogram parameters to determine optimal values for sequencing the process on a daily basis. The program then determines the best fit based on our initial input of the sill, range, and nugget by using ordinary least square regression of the variogram parameter in sequence for the whole year. These models were then tested and the root mean square error (RMSE) of the cross validation was used to test and compare spatial statistics among days in 2008.The model and variogram parameters with the closest RMSE to zero were used as the model that fits the variogram best.

RESULTS

Table II-1 presents summary descriptive statistics for air pollutants using the available monitoring sites: 14 (PM_{10}), 9 ($PM_{2.5}$), 22 (O_3), 18 (NO_2), 17 (CO), and 26 (SO_2) during all of 2008 and within the dry and wet seasons. Overall, means and standard deviations for the different metrics were similar within each pollutant across the 2008 study period. Maximum daily averages determined by NM, IDW, and OK were higher when compared to the maximums computed by CWA. Maximum PM_{10} concentrations were higher in the northern part of Mexico City. On the other hand,, $PM_{2.5}$ concentrations were spatially homogenous throughout Mexico City. O_3 concentrations were higher in the southern region. All other pollutants follow a relative homogenous distribution across the area of study and across estimates produced for the overall study period. Examination of seasonal distribution of exposure metrics showed that days with the maximum concentrations occurred during the dry season for all exposure assessment methods. During the wet season, the ranges of estimates produced from spatially explicit exposure assessment methods were higher than for the CWA metrics. Overall, the pollutants analyzed, with the exception of SO_2 and CO, had concentration levels that surpass most air quality standards and guidelines established by U. S. regulatory agencies and international agencies (Table II-S4).

Table II-2 shows Pearson correlation coefficients among all air pollutants by exposure assessment method. In table II-3, as expected, the two most highly correlated methods were the IDW and OK which are both weighted averaging methods. Consistently, the correlations between all the pollutants was highest for CWA and

lowest for NM, which is what would be expected since no averaging is applied to the NM method, and the assumption is the person is exposed to the concentration of pollution measured at the single monitor nearest her residence. The correlations for the interpolation methods were always lower between the NM and CWA for each of the pollutant pairs.

Model evaluation

Models were compared by examining correlation coefficients across exposure metrics constructed for each exposure assessment method. Table II-3 shows Pearson's correlation coefficients for pairs of methods across all air pollutants. The correlation coefficients among exposure methods for all criteria pollutants were generally high (0.77 to 0.99). All pollutant estimates produced by OK, with the exception of SO_2, were highly correlated with estimates produced by CWA. NM correlations with other methods were always the smallest, again because no averaging with data from other monitors is employed in that method compared to the three others.

Pearson correlation coefficients were calculated between exposure assessment methods and each air pollutant for all five zones (Table II-4a-4f). Zone 5 covers the north of Mexico City, where zone 1, 2, 3, and 4 cover the center, east, south, and west, respectively. Correlation coefficients were relatively high between methods for all pollutants, except for correlations between CWA and NM. When looking at all zones, except for the southern zone, CO showed high correlations between methods (r=0.77-0.96). NO_2 exhibited high correlations between methods for all zones, except for the correlations between CWA and NM. Correlation coefficients for O_3 in the north and center zones showed lower correlations when compared to CWA and NM. PM_{10} and

$PM_{2.5}$ had high correlations when all zones were examined, although for $PM_{2.5}$ the southeast and west zones showed lower correlations when looking at associations between CWA, NM, and OK. Lastly, SO_2 shows smaller correlation coefficients when looking at the southeast, south, west, and northwest zones than other pollutants, where IDW and CWA have higher correlation than CWA with NM and OK.

We also examined the range of estimates across all pollutants and zones by computing the differences between the interpolated methods results (i.e., means and standard deviation) (Table II-5). Using OK as the 'gold standard', in northern zone (Zone 5) of the city (high PM_{10}), CWA and IDW underestimated PM_{10} on average by 4.17 and underestimated by 1.80 $\mu g/m^3$, respectively, and NM overestimated the exposure by 4.11 $\mu g/m^3$ when compared to OK. In the south (Zone 3), CWA overestimated PM_{10} exposure by7.49 $\mu g/m^3$, whereas NM and IDW underestimated the exposure by 3.09 $\mu g/m^3$ and 7.21 $\mu g/m^3$, respectively. IDW methodology was able to produce lower standard deviations of the mean difference for the north and south zones. The center and eastern zone (zone 1 and 2, respectively) of the Mexico City exhibit minimal differences in PM_{10} estimates for the four methods. For $PM_{2.5,}$ estimated metrics were relatively similar across methods and zones. In southern zone (high O_3), CWA underestimated the exposure by 0.91and IDW by 3.29 ppb, whereas NM overestimated the exposure by 4.18 ppb. IDW estimates produced higher SD when looking at the mean difference between methods. All other pollutants, i.e., NO_2, CO, and $SO_{2,}$ produced similar estimates when comparing among all three methods. Estimates produced by IDW showed higher standard deviations than other methods examined in this study.

When looking at individuals who were restricted by pollutant-specific polygons, standard errors were approximately equal in magnitude (Table II-6).

Table II-7 reports ordinary kriging cross validation root means square errors (RMSE) for the different air pollutants. Mean RMSE values calculated were similar between air pollutants. This shows that OK performed about the same in estimating actual concentrations for all pollutant types during the study period. We conducted cross=validation for methods that showed spatial variation (interpolation methods) in the estimates produced for PM_{10} and O_3. RMSEs for PM_{10} were 16.00 and 13.34 for NM and IDW, respectively. On the other hand, RMSEs for O_3 were 14.08 and 10.08 for NM and IDW respectively. OK RMSEs for PM_{10} and O_3 were significantly lower than the ones estimated by NM and IDW.

Descriptive statistics for all pollutants and individuals who reside within pollutant-specific polygons are shown in Table II-8. Mean concentrations were relatively smaller than mean concentrations produced for all 1,000 individuals across Mexico City. When examining the range of concentrations produced for all methods and pollutants, maximum concentrations estimated by OK were lower, except for NO_2 and CO. PM_{10} and $PM_{2.5}$ show significantly lower predicted concentrations, when compared to NM and IDW. This could be because the restriction to women within the polygons tends to disproportionately retain women living in lower pollution areas.

DISCUSSION AND CONCLUSION

Air pollution exposure assessments in epidemiological studies frequently rely on simple spatial averaging methods for the determination of possible individual exposure to airborne contaminants. GIS and geostatistical interpolation methods have

been used to predict exposures at unsampled locations (Liao, Peuquet et al. 2006; Brauer, Lencar et al. 2008; Son, Bell et al. 2010). The main aim of this study was to develop exposure assessment methods (CWA, NM, IDW, and OK) to estimate daily individual exposure for 1,000 simulated individuals in Mexico City during 2008 and evaluate differences in metrics produced and accuracy of prediction by descriptive statistics, correlations, and cross validation statistics. This aim was fulfilled by examining the range and correlations of concentrations produced by the different methods examined in this study. This wide range of exposure metrics ensures that for the simulated 1,000 individuals and future studies in Mexico City a gradient of temporal and spatial variation of air pollution exposures is allocated in the study design when recruiting participants. The power of an environmental epidemiology study to detect associations depends in part on having an adequate gradient of exposure in the population of interest (Navidi, Thomas et al. 1999).

The four exposure assessment methods yielded similar, but not identical, results for the air pollutants examined. The ranges of exposure metrics produced by the methods that incorporated geo-referenced location data of individuals were significantly higher in comparison to estimates produced by the CWA approach. A cohort study which produced exposure metrics for a Korean population utilized similar exposure assessment methods to our study and found that the exposure assessment produced similar estimates for different air pollutants and that the ranges of concentrations from methods which included geographical location were higher than those which were made by spatial averaging (Son, Bell et al. 2010). This shows the importance of spatial heterogeneity of the studied contaminants. In addition,

researchers have found that interpolation methods produce similar estimates to averaging methods when the monitor density was low, whereas in other places where monitor density is high the differences are much higher (Wong, Yuan et al. 2004). High correlation coefficients between OK and IDW suggest that these two interpolation methods were similarly able to predict spatial gradients in concentrations of air pollutants.

The NM and IDW methods are much simpler in their calculation than OK. Air pollution exposure estimation by OK offers its challenges. One of the challenges involves dealing with empirical and experimental variogram estimation. We found that in order to automate and optimize the daily estimation of variogram parameters (range, sill, and nugget), skewed air pollution data needed to be log-transformed (Liao, Peuquet et al. 2006). Also, to select the best-fitting model, based on cross validation exercises, variogram parameters needed to be determined by exploring their RMSE values under different covariance models (spherical, exponential, and Gaussian). For all air pollutants, the spherical covariance model showed the lowest RMSE. This finding is supported by other research which experimented with model fit and settled on the spherical model (Son, Bell et al. 2010). Universal kriging, which accounts for spatial trends, was determined to produce cross validation results with higher RMSE than the OK method. Thus, we determined that ordinary kriging, which assumes a constant mean, would be a more conservative method.

The development of different exposure assessment methodologies that use all available air pollution monitoring sites for estimating concentrations for georeferenced data from 1,000 simulated individuals in Mexico City's metropolitan area are major

strengths of this study. Considering that Mexico City is a megacity, geocoding positional errors, which are more likely in rural settings, are of little concern in the population of study or in future geo-referenced data from the city (Ward, Nuckols et al. 2005).

As far as we know this is the first study to examine differences in air pollution exposure metrics produced by commonly used exposure assessment methods in Mexico City. Advantages in this study include our ability to exploit both the temporal and spatial scale of the air pollution data derived from the monitoring network, the ability to compare different exposure assessment methodologies, the creation of future capacity for linking the metrics with an ongoing birth cohort, and, because of the use of methods to calculate daily exposures, the ability to calculate an indefinite number of windows of exposure during pregnancy, not limited to trimesters which may not capture the biologically relevant times of exposure.

Some of the limitations include the fixed number of available monitors (e.g. $PM_{2.5}$) which are essential to improve model performance, and lacking 'true' personal exposure measurements as a gold standard. Nevertheless, previous work suggests that outdoor monitor concentrations are well-correlated with indoor and personal measures of exposure to air pollution in Mexico City (Rojas-Bracho 1994; O'Neill, Ramirez-Aguilar et al. 2003). The results of this study may not apply to all other geographical locations, since environmental and housing characteristics of different geographical settings may affect air pollution exposures. However, similar patterns could be seen in other megacities in temperate climates, where air conditioning and heating are not highly prevalent.

Examining the spatial variation in air pollution exposure, especially in a geographical setting like Mexico City with its "bowl-shape" geography, which promotes the accumulation of pollutants and the formation of gradients of some of the air pollutants, is important for epidemiological studies. Earlier studies examining particulate exposure have shown gradients of exposure that vary by size and chemical composition in Mexico City (Osornio-Vargas, Bonner et al. 2003). In this study period, we observed levels of air pollution exceeding Mexico City air quality standards, the United States Environmental Protection Agency (USEPA), and World Health Organization (WHO) (Table III-S4). This suggests that air pollution is a continuing threat to the health of the population there; PM_{10} and O_3 were the two pollutants most frequently exceeding these standards.

Seasonal differences in air pollution are of critical interest for perinatal epidemiology due to the relation that season has with preterm birth and other covariates of interest. Air pollution exposure has been associated with the duration of pregnancy, so it has been recommended that researchers control for the season of conception instead of season of birth when assessing air pollution associations with birth outcomes (Slama, Darrow et al. 2008; Woodruff, Parker et al. 2009). In this case, season could be a potential confounder since preterm rates are higher in certain seasons, and air pollution exposures are also higher in certain seasons.

The findings of our exercise in comparing air pollution exposure assessment metrics suggest that the power of perinatal epidemiology studies in Mexico City can be greatly enhanced by knowing the location where women spend their time, enabling the estimation of exposure with not only a temporal but a spatial gradient, and thus

maximizing exposure contrasts. Second, our results suggest that OK and IDW are interpolation methods that yielded similar estimated exposures among the simulated women. Third, our results suggest that the zone of Mexico City in which women live can affect how well different exposure metrics correlate. This suggests that measurement error may have variable magnitude depending on zone, especially when using a method like CWA. Further, factors that could be relevant to preterm risk could also differ by zone and thus disentangling the contribution of exposure measurement error from confounding by these other factors could present a challenge.

In conclusion, geostatistical methods to estimate pollution exposure using data from an air monitoring network can be applied when information on spatial location and activity patterns from participants in epidemiology studies is gathered. These exposure estimation methods can be combined with biomarker data, personal exposure measures, and more complex modeling approaches such as land-use regression, to better understand how air pollution influences health and to set control and prevention priorities

Figure II-1. Location of simulated subjects' residences, Thiessen polygons and air quality monitors in Mexico City.

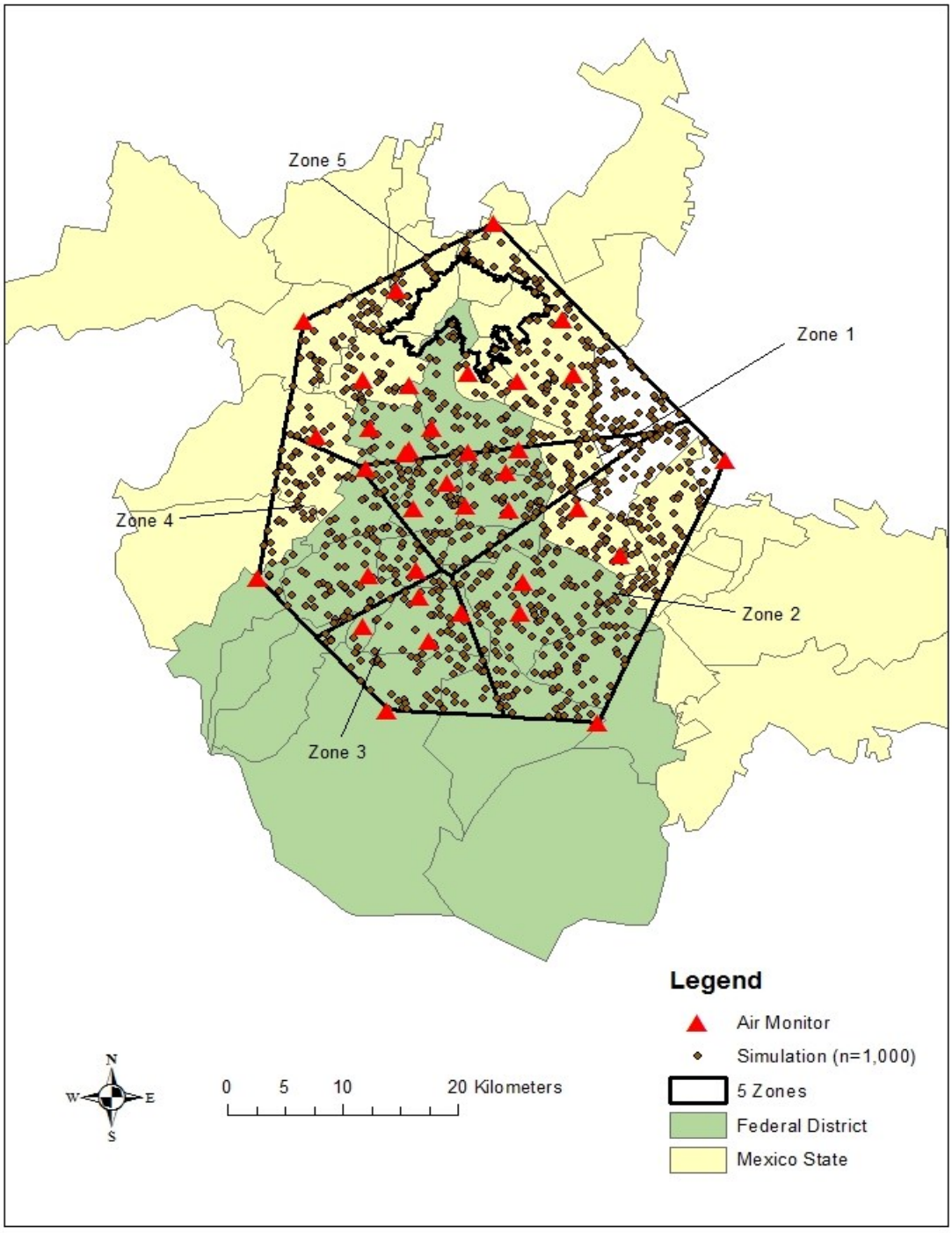

Table II-1. Descriptive statistics for four exposure metrics calculated for 1,000 simulated residents of Mexico City using daily concentrations of air pollutants during calendar year 2008.

Air Pollutant		Entire year 2008		Dry Season[1]		Wet Season[2]	
(n Monitors)	Method	Mean (S.D)	Range	Mean (S.D)	Range	Mean (S.D)	Range
PM_{10} ($\mu g/m^3$)	CWA	53.20 (20.6)	14.4 - 109.7	67.8 (15.4)	20.7 -109.7	38.8 (13.9)	14.4 - 88.0
14 Sites	NM	53.7 (25.4)	8.0 - 214.1	68.9 (23.8)	15.1 - 214.1	38.7 (16.6)	8.0 - 122.5
	IDW	49.9 (21.7)	0.1 - 209.4	61.6 (20.7)	0.1 - 209.4	38.4 (15.6)	0.3 - 120.5
	OK	52.9 (22.8)	8.4 - 206.7	67.8 (19.5)	15.7 - 206.7	38.1 (14.8)	8.4 - 113.2
$PM_{2.5}$ ($\mu g/m^3$)	CWA	26.8 (10.1)	7.7 - 67.0	32.4 (8.3)	9.2 - 67.0	21.4 (8.7)	7.7 - 52.5
9 Sites	NM	27.6 (13.0)	4.5 - 110.3	33.7 (12.5)	6.2 - 110.3	21.6 (10.5)	4.5 - 91.3
	IDW	26.6 (11.6)	0.1 - 110.1	32.0 (10.9)	0.2 - 110.1	21.4 (9.6)	0.2 - 91.1
	OK	26.3 (10.0)	5.6 - 102.4	31.6 (8.2)	6.5 - 102.4	21 (8.6)	5.6 - 82.6
O_3 (ppb)	CWA	58.0 (18.5)	12.7 - 113.3	61.6 (16.5)	22.7 - 98.3	54.4 (19.6)	12.7 - 113.3
22 Sites	NM	56.8 (21.3)	3.5 - 160.3	60.5 (20)	3.5 - 127.4	53.1 (21.9)	4.0 - 160.3
	IDW	53.9 (19.9)	0.1 - 151.5	56.4 (18.7)	0.5 - 127.3	51.4 (20.8)	0.1 - 151.5
	OK	56.6 (19.0)	5.4 - 134.5	60.3 (17.1)	6.7 - 127.3	52.9 (20.0)	5.4 - 134.5
NO_2 (ppb)	CWA	30.6 (9.3)	10.7 - 62.4	35.6 (9.4)	16.1 - 62.4	25.7 (6.0)	10.7 - 48.8
18 Sites	NM	30.3 (10.9)	3.2 - 79.2	35.0 (11.2)	3.5 - 79.2	25.7 (8.2)	3.2 - 70.7
	IDW	29.7 (10.2)	0.1 - 78.6	33.2 (11.1)	0.1 - 78.6	26.2 (7.6)	0 - 69.0
	OK	29.7 (10.0)	3.5 - 78.9	34.8 (9.9)	4.8 - 78.9	24.7 (7.0)	3.5 - 70.0
CO (ppm)	CWA	1.5 (0.6)	0.4 - 3.5	1.9 (0.6)	0.5 - 3.5	1.2 (0.4)	0.4 - 2.3
17 Sites	NM	1.6 (0.8)	0.1 - 5.5	1.9 (0.8)	0.1 - 5.5	1.2 (0.6)	0 - 3.6
	IDW	1.4 (0.6)	0.01 - 5.4	1.7 (0.7)	0 - 5.4	1.2 (0.4)	0 - 3.5
	OK	1.5 (0.6)	0.2 - 5.0	1.9 (0.6)	0.2 - 5.0	1.2 (0.4)	0.1 - 3.6
SO_2 (ppb)	CWA	6.7 (5.1)	2.3 - 33.9	8.0 (6.1)	2.5 - 33.9	5.4 (3.5)	2.3 - 22.1
26 Sites	NM	6.4 (6.3)	1.0 - 164.3	7.5 (7.6)	1.0 - 164.3	5.3 (4.4)	1.0 - 49.1
	IDW	5.8 (5.3)	0 - 162.7	6.7 (6.5)	0 - 162.7	4.8 (3.6)	1.0 - 49.1
	OK	6.0 (5.3)	0.9 - 153.0	7.0 (6.3)	1.0 - 153.0	4.9 (3.7)	0.9 - 43.3

Footnote: [1]Dry Season (November - April); [2]Wet Season (May - October). Mexico City standards: PM 10 (Annual Mean - 50 µg/m3; Daily Average - 120 µg/m3); $PM_{2.5}$ (Annual Mean - 15 $\mu g/m^3$; Daily Average - 65 $\mu g/m^3$);O3 (1-h average - 110 ppb; 8-hr average - 80 ppb); SO2 (Annual Mean - 30 ppb; Daily Average - 130 ppb); NO2 (1hr Average - 210 ppb); CO (8- hr Average - 11ppm). Abbreviations: CWA=Citywide average; NM = Nearest Monitor; IDW=Inverse DistanceWeighting; OK=Ordinary Kriging; Std. Dev=Standard Deviation; min=Minimum; max=Maximum

Table II-2. Pearson correlation coefficients among air pollutants in Mexico City during 2008 by method used to assign exposure to 1,000 simulated residents (n=366,000)

Citywide Average Method	PM_{10}	$PM_{2.5}$	O_3	NO_2	SO_2
$PM_{2.5}$	0.88				
O_3	0.54	0.65			
NO_2	0.74	0.70	0.40		
SO_2	0.39	0.37	0.14	0.30	
CO	0.70	0.63	0.23	0.85	0.15

Nearest Monitor Method	PM_{10}	$PM_{2.5}$	O_3	NO_2	SO_2
$PM_{2.5}$	0.66				
O_3	0.32	0.48			
NO_2	0.53	0.50	0.30		
SO_2	0.24	0.23	0.07	0.19	
CO	0.50	0.47	0.17	0.68	0.08

Inverse Distance Weighting	PM_{10}	$PM_{2.5}$	O_3	NO_2	SO_2
$PM_{2.5}$	0.78				
O_3	0.43	0.57			
NO_2	0.64	0.63	0.38		
SO_2	0.33	0.31	0.10	0.24	
CO	0.62	0.56	0.21	0.79	0.11

Ordinary Kriging Method	PM_{10}	$PM_{2.5}$	O_3	NO_2	SO_2
$PM_{2.5}$	0.81				
O_3	0.46	0.62			
NO_2	0.65	0.66	0.35		
SO_2	0.30	0.32	0.12	0.26	
CO	0.63	0.60	0.21	0.79	0.12

All p-values <0.0001

Table II-3. Pearson correlation coefficients among four metrics estimating the exposure of 1,000 simulated women to six different air pollutants in Mexico City, 2008. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		PM_{10}	
NM	0.83		
IDW	0.92	0.95	
OK	0.92	0.94	0.98
		$PM_{2.5}$	
NM	0.83		
IDW	0.93	0.95	
OK	0.99	0.84	0.94
		O_3	
NM	0.85		
IDW	0.94	0.95	
OK	0.96	0.91	0.97
		NO_2	
NM	0.82		
IDW	0.93	0.94	
OK	0.93	0.91	0.97
		CO	
NM	0.77		
IDW	0.91	0.92	
OK	0.94	0.85	0.96
		SO_2	
NM	0.77		
IDW	0.88	0.95	
OK	0.83	0.93	0.97

Table II-4a. Pearson correlation coefficients among exposure assessment methods stratified by zone for CO in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.79		
IDW	0.94	0.90	
OK	0.93	0.86	0.98
		Zone 2	
NM	0.80		
IDW	0.95	0.90	
OK	0.97	0.83	0.96
		Zone 3	
NM	0.59		
IDW	0.84	0.84	
OK	0.91	0.71	0.92
		Zone 4	
NM	0.70		
IDW	0.89	0.89	
OK	0.93	0.81	0.96
		Zone 5	
NM	0.84		
IDW	0.93	0.96	
OK	0.95	0.91	0.97

Table II-4b. Pearson correlation coefficients among exposure assessment methods stratified by zone for NO_2 in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.84		
IDW	0.96	0.93	
OK	0.94	0.90	0.98
		Zone 2	
NM	0.85		
IDW	0.96	0.92	
OK	0.96	0.89	0.96
		Zone 3	
NM	0.77		
IDW	0.91	0.93	
OK	0.92	0.89	0.97
		Zone 4	
NM	0.91		
IDW	0.97	0.97	
OK	0.96	0.95	0.98
		Zone 5	
NM	0.81		
IDW	0.92	0.94	
OK	0.92	0.92	0.97

Table II-4c. Pearson correlation coefficients among exposure assessment methods stratified by zone for O_3 in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.88		
IDW	0.96	0.95	
OK	0.97	0.92	0.98
		Zone 2	
NM	0.84		
IDW	0.96	0.92	
OK	0.97	0.89	0.97
		Zone 3	
NM	0.90		
IDW	0.96	0.97	
OK	0.96	0.94	0.98
		Zone 4	
NM	0.92		
IDW	0.96	0.97	
OK	0.97	0.95	0.98
		Zone 5	
NM	0.83		
IDW	0.92	0.95	
OK	0.95	0.90	0.96

Table II- 4d. Pearson correlation coefficients among exposure assessment methods stratified by zone for PM_{10} in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.92		
IDW	0.98	0.96	
OK	0.97	0.95	0.99
		Zone 2	
NM	0.91		
IDW	0.98	0.95	
OK	0.97	0.94	0.98
		Zone 3	
NM	0.90		
IDW	0.96	0.96	
OK	0.93	0.94	0.98
		Zone 4	
NM	0.87		
IDW	0.95	0.95	
OK	0.92	0.94	0.98
		Zone 5	
NM	0.84		
IDW	0.93	0.95	
OK	0.91	0.93	0.97

Table II-4e. Pearson correlation coefficients among exposure assessment methods stratified by zone for $PM_{2.5}$ in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.92		
IDW	0.97	0.97	
OK	0.99	0.93	0.97
		Zone 2	
NM	0.83		
IDW	0.92	0.94	
OK	0.99	0.83	0.92
		Zone 3	
NM	0.91		
IDW	0.96	0.97	
OK	0.99	0.92	0.97
		Zone 4	
NM	0.88		
IDW	0.97	0.95	
OK	0.99	0.88	0.98
		Zone 5	
NM	0.91		
IDW	0.96	0.98	
OK	0.99	0.92	0.97

Table II-4f. Pearson correlation coefficients among exposure assessment methods stratified by zone for SO_2 in 2008. 200 women in each zone, all p-values < 0.0001. (n=366,000)

	CWA (N)	NM (N)	IDW (N)
		Zone 1	
NM	0.86		
IDW	0.95	0.95	
OK	0.91	0.95	0.98
		Zone 2	
NM	0.80		
IDW	0.93	0.92	
OK	0.86	0.87	0.93
		Zone 3	
NM	0.82		
IDW	0.91	0.96	
OK	0.89	0.93	0.97
		Zone 4	
NM	0.80		
IDW	0.91	0.95	
OK	0.87	0.93	0.97
		Zone 5	
NM	0.77		
IDW	0.88	0.95	
OK	0.84	0.93	0.98

Table II-5. Mean difference and standard deviations (SD) of the differences in air pollution exposure estimates produced by three exposure assessment methodologies for 1,000 simulated women in Mexico City during 2008, with kriging as the reference method.

		Mean Difference (SD)					
Zone	Model	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)	O_3 (ppb)	NO_2 (ppb)	CO (ppm)	SO_2 (ppb)
All Zones	CWA	0.34 (9.03)	0.56 (1.04)	1.40 (5.43)	0.88 (3.61)	-0.03 (0.20)	0.71 (3.03)
	NM	0.84 (8.96)	1.36 (7.10)	0.20 (9.06)	0.59 (4.53)	0.02 (0.40)	0.42 (2.44)
	IDW	-2.3 (12.2)	0.38 (5.10)	-2.68 (8.29)	-0.07 (6.02)	-0.10 (0.34)	-0.18 (1.97)
1	CWA	-1.14 (5.83)	0.61 (0.94)	1.94 (4.67	-1.53 (3.77)	-0.11 (0.24)	0.59 (2.19)
	NM	1.75 (7.37)	0.13 (3.57)	-1.30 (8.17)	1.69 (5.07)	0.18 (0.40)	0.21 (2.02)
	IDW	-3.40 (10.8)	-0.12 (3.11)	-2.62 (5.85)	1.03 (3.42)	0.01 (0.22)	-0.27 (1.75)
2	CWA	0.94 (5.52)	0.43 (1.48)	0.97 (4.68	1.05 (2.71)	-0.01 (0.14)	1.57 (2.81)
	NM	0.08 (7.99)	4.95 (10.23)	1.57 (9.25)	1.14 (4.54)	0.08 (0.40)	0.24 (2.15)
	IDW	-2.50 (9.83)	2.46 (7.52)	-4.22 (8.71)	0.19 (6.54)	-0.13 (0.36)	-0.21 (1.71)
3	CWA	7.49 (7.47)	0.76 (0.90)	-0.91 (5.82)	0.72 (3.67)	0.09 (0.24)	0.97 (2.37)
	NM	-3.09 (5.91)	-2.78 (3.87)	4.18 (8.54)	0.94 (4.55)	-0.20 (0.45)	0.41 (1.86)
	IDW	-7.21 (14.0)	-2.31 (3.49)	-3.29 (13.2)	-2.40 (11.1)	-0.30 (0.55)	-0.64 (2.35)
4	CWA	7.26 (7.95)	0.65 (0.49)	-0.23 (4.82)	1.18 (2.83)	0.03 (0.22)	0.18 (2.76)
	NM	-3.62 (6.31)	-0.92 (4.69)	2.56 (7.64)	0.71 (3.28)	0.05 (0.40)	0.64 (2.24)
	IDW	-3.40 (5.57)	-1.22 (2.96)	0.33 (6.4)	0.76 (3.04)	-0.05 (0.26)	0.14 (1.75)
5	CWA	-4.17 (10.5)	0.58 (0.71)	2.83 (6.03)	1.70 (4.02)	0.01 (0.19)	0.12 (3.55)
	NM	4.11 (10.5)	-0.59 (4.24)	-2.39 (9.05)	-0.54 (4.45)	-0.05 (0.32)	0.59 (3.55)
	IDW	-1.80 (15.5)	0.01 (2.84)	-2.30 (7.36)	-0.50 (5.08)	0.10 (0.29)	-0.12 (2.22)

Note: Zone 1=Center; Zone 2=East; Zone 3=South; Zone 4=West; Zone 5=North. Negative values reflects overestimation by the exposure method being compared to ordinary kriging.

Table II-6. Descriptive statistics of the standard errors (SE) among individuals residing inside pollutant specific polygons in 2008 in Mexico City.

Pollutant	N	Mean	SD	Min	Max
PM_{10} ($\mu g/m^3$)	189,222	9.58	4.85	0.48	64.9
$PM_{2.5}$ ($\mu g/m^3$)	154,452	38.2	15.0	3.35	100.0
O_3 (ppb)	319,884	10.3	7.58	0.58	107.5
NO_2 (ppb)	163,236	4.57	1.65	0.45	14.2
CO (ppm)	140,910	0.41	0.11	0.07	1.06
SO_2 (ppb)	308,904	2.37	1.75	0.11	53.8

Table II-7. RMSEs reported by cross validation analysis during 2008 for each air pollutant using ordinary kriging estimates.

Pollutant	Mean (SD)	Median	Range (Min - Max)
PM_{10}	1.25 (0.08)	1.23	1.08 - 1.59
$PM_{2.5}$	1.26 (0.09)	1.25	1.09 - 1.70
O_3	1.24 (0.13)	1.22	1.07 - 1.93
NO_2	1.25 (0.095)	1.22	1.07 - 1.65
CO	1.64 (0.24)	1.60	1.22 - 2.72

Note: RMSE's produced daily for the period of 2008 by application of spherical ordinary kriging.

Abbreviations: SD=Standard Deviation; Min=Minimum; Max=Maximum

Table II-8. Descriptive statistics for each pollutant for individuals living inside pollutant specific polygons in 2008 in Mexico City.

Pollutant	Method	N	Mean	SD	Min	Max
PM_{10} ($\mu g/m^3$)	CWA	189,222	53.2	20.6	14.4	109.7
	NM	189,210	55.1	25.7	8.0	214.1
	IDW	189,222	50.6	21.9	8.2	206.4
	OK	189,222	53.6	22.8	8.4	194.4
$PM_{2.5}$ ($\mu g/m^3$)	CWA	154,452	26.8	10.1	7.7	67.0
	NM	154,452	27.0	12.0	4.5	110.3
	IDW	154,452	26.2	10.8	4.6	108.8
	OK	154,452	26.2	9.9	5.6	88.2
O_3 (ppb)	CWA	319,884	58.0	18.5	12.7	113.3
	NM	319,860	57.1	21.4	3.5	160.3
	IDW	319,518	53.8	20.0	4.5	151.5
	OK	319,884	56.7	19.0	5.4	134.5
CO (ppm)	CWA	140,910	1.54	0.58	0.44	3.45
	NM	140,886	1.66	0.77	0.07	5.47
	IDW	140,910	1.53	0.68	0.08	5.39
	OK	140,910	1.58	0.64	0.19	4.99
NO_2 (ppb)	CWA	163,236	30.6	9.3	10.7	62.4
	NM	163,223	32.3	11.6	3.2	79.2
	IDW	163,236	30.4	10.6	3.6	78.6
	OK	163,236	31.0	10.4	3.5	78.9
SO_2 (ppb)	CWA	308,904	6.67	5.12	2.29	33.89
	NM	308,461	6.30	6.32	1.00	16.43
	IDW	308,904	5.72	5.36	1.00	16.27
	OK	308,904	5.92	5.28	0.09	15.30

Note: These summary statistics are the averages for groups of individuals who lived inside pollutant specific polygons.

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CHAPTER III

ASSOCIATION OF AIR POLLUTION AND PRETERM BIRTH IN MEXICO CITY: IMPLICATIONS OF DIFFERENT EXPOSURE ASSESSMENT METHODOLOGIES

INTRODUCTION

The growing rate of preterm birth and its contribution to infant mortality and morbidity constitute a major health problem in the United States as well as in other parts of the world, especially developing countries (Martin, Kung et al. 2008). Recent studies have identified outdoor air pollution as a possible risk factor for reproductive disorders (e.g. preterm birth, intrauterine growth restriction (IUGR), and low birth weight (LBW)) (Glinianaia, Rankin et al. 2004; Maisonet, Correa et al. 2004; Sagiv, Mendola et al. 2005; Sram, Binkova et al. 2005; Wilhelm and Ritz 2005; Huynh, Woodruff et al. 2006; Ritz, Wilhelm et al. 2007; Ritz and Wilhelm 2008; Slama, Darrow et al. 2008; Stillerman, Mattison et al. 2008; Yorifuji, Naruse et al. 2011; Le, Batterman et al. 2012). Preterm births (births that occur at less than 37 weeks of gestation) have been associated with many factors including individual-level behavioral and psychosocial factors, neighborhood characteristics, environmental exposures, medical conditions, infertility treatment, biological factors, and genetics (Berkowitz and Papiernik 1993; Hoffman and Hatch 1996; Zeitlin, Saurel-Cubizolles et al. 2002; Da Silva, Simões et al. 2003; IOM 2007; Savitz and Murnane 2010).

Much research pertaining to air pollution and preterm birth outcomes has relied on combining data from large birth registries with air pollution concentrations obtained from outdoor air quality monitors to estimate individual exposure. Due to the high degree of spatial variability of different measured data from monitors, interest has grown in creating spatial and temporal models to predict exposure for people whose residential location is known without having to obtain personal exposure monitoring data (Woodruff, Parker et al. 2009).

Recent interest in preterm birth has sparked new scientific research, as well as recognition from governmental entities and the scientific community on the importance of identifying and learning more about how environmental toxicants may influence preterm birth. Researchers around the world agree upon the need to identify differences in methodologies used among previous epidemiological studies of air pollution and perinatal health outcomes (Sram, Binkova et al. 2005; Slama, Darrow et al. 2008; Woodruff, Parker et al. 2009).

Previous studies of the association between air pollutants and preterm birth have not found conclusive or consistent associations during different windows of exposure in pregnancy. Moreover, few studies have been able to explore different exposure assessment methods for estimating individual exposure to air pollutants, especially during pregnancy (Nethery, Leckie et al. 2008; Perera, Li et al. 2009). The purpose of this paper is to use three methods (citywide averaging, nearest monitor, and inverse distance weighting) to estimate daily individual exposure to outdoor air pollution during pregnancy among women who participated in a cohorts studies in Mexico City, to identify which windows of exposure might be more strongly

associated with preterm birth, and to assess whether these different exposure assessment methods produce different associations with preterm birth

METHODS

Study Population

The study population was recruited at three different hospitals in Mexico City during 1994 to 2004 as part of the ELEMENT (Early Life Exposure in Mexico to Environmental Toxicants) study (http://sitemaker.umich.edu/merg/element) (Gonzalez-Cossio, Peterson et al. 1997; Tellez-Rojo, Hernandez-Avila et al. 2004; Lamadrid-Figueroa, Tellez-Rojo et al. 2007). This study is based on a population recruited for a series of epidemiological birth cohorts that had the overall purpose of study how cumulative lead exposure relates to certain perinatal health outcomes and infant health.

Participants attending these hospitals are from a low-to-moderate-income population, lived in Mexico City metropolitan area during the time of their participation in the study.

Exclusion criteria for the main and subsequent cohorts included risk factors related to calcium metabolism, medical conditions that could cause low birth weight (<2500 grams), delivering premature (<37 weeks), a physician's diagnosis of multiple fetuses, preeclampsia, kidney, psychiatric or cardiac conditions, gestational diabetes, history of repeated urinary infections, and seizure conditions that would require medication (Tellez-Rojo, Hernandez-Avila et al. 2004; Hu, Tellez-Rojo et al. 2006; Lamadrid-Figueroa, Tellez-Rojo et al. 2007).

All cohort participants signed an informed consent before enrolling in the study. The research protocols were approved by the Ethics and Research Committee or Institutional Review Boards (IRB) of the National Institute of Public Health (Cuernavaca, Mexico City), the Harvard School of Public Health, the Brigham and Women's Hospital, the University of California, and participating hospitals. The present analysis was approved by the University of Michigan IRB.

For the present study, gestational age was determined by the mother's recall of her last menstrual period (LMP) since ultrasound information was not collected at participating hospitals. Using the estimated gestational age and the infant's date of birth, the infant's date of conception was calculated. Preterm birth was defined as live births occurring before 38 weeks of gestation. Other variables determined *a priori* to be of interest as potential confounders of the preterm and air pollution association were derived from questionnaire data. These include mother's age, smoking frequency, educational attainment, marital status, infant sex, and parity. These variables have been associated with preterm birth in previous studies.

Additionally, calf circumference, measured approximately during the 10 month post-partum visit to the clinics, was used to estimate maternal nutritional status during pregnancy. Although other variables, such as body mass index, have been used for this purpose, calf circumference was the variable available for the majority of the cohort participants.

Geo-coding of Study Participants

Retrospectively, based on the street address recorded on study forms, participants were assigned a latitudinal and a longitudinal coordinate through the use

of "Guia Roji Global Positioning Atlas" mapping software (http://www.guiaroji.com.mx/). Geocoordinates were validated by project drivers who were familiar with Mexico City and the women's residences, in some cases; these drivers also updated some of the recorded addresses which could not be coded due to lack of information. After the validation, the geo-coordinates were digitized into maps through the use of ArcGIS (version 9.3.1) (ESRI Inc., Redlands, CA).

A total of 2098 participants had their residential addresses geo-referenced. Cohort 1 participants were excluded from the current analysis due to the fact that having a preterm delivery was one of the exclusion criteria for that cohort.. The remainder of the women were included in the study after excluding participants who were missing infant's date of birth or gestational age, smoking status during pregnancy, and post-partum calf circumference measurement.

Air pollution Data and Exposure Assessment Methods

The air quality monitoring network in Mexico City ("Sistema de Monitoreo Atmosférico", or SIMAT by its acronym in Spanish) consists of 36 stations that measure different pollutants throughout the metropolitan area. Of these 36 sites, 22 sample for ozone and 26 for PM_{10}, (Zuk, Tzintzun Cervantes et al. 2007). We downloaded hourly data from the automated air monitoring network on December 9, 2009 for the calendar years (1997-2005). Prior to posting on the website, SIMAT staff cleaned and validated the data (Zuk, Tzintzun Cervantes et al. 2007; Retama-Hernandez 2011). PM_{10} was measured in units of micrograms per cubic meter ($\mu g/m^3$), whereas O_3, was measured in parts-per-million (ppm) when the data was downloaded from the governmental agency. O_3, data was transformed from parts-per-million to

parts-per-billion (ppb) to be consistent with Mexico City air pollution standards. For PM_{10}, we retained the original units reported by SIMAT. Although data are available hourly for most of the pollutants, we summarized data to match the averaging time of the Mexican standards: daily concentrations (24 hour averages) of PM_{10} and the daily 8 hour maximum for O_3, from all available monitoring stations. If more than 25% of the hourly pollutant concentration in a given day were missing, the daily concentration was coded as 'missing'.

Geographical coordinates for the monitoring stations were provided by SIMAT and digitized into a layer of information in order to combine with the women's residential locations using ArcGIS (version 9.3.1) (ESRI Inc., Redlands, CA).

Daily citywide averages were calculated using all available reporting monitors for a specific day. For each of the women, nearest monitor averages were produced for each day, and for each air pollutant using the closest distance, determined by a straight line, from the participant's residence to the monitor closest to the participant. In the case that the nearest monitor did not have reporting data, the next closest monitor would provide the concentration value for that particular day. Inverse distance squared interpolation averages were produced using a minimum of 5 monitors and a maximum of 12 monitors closest to the individual's residential location. All metrics were produced using the Statistical Analysis System (SAS version 9.2; SAS Institute, Inc. Cary, NC).

Exposure Window Calculation

Air pollution concentration averages were created for the entire period of duration of pregnancy, and first, second, and third trimesters. First trimester averages

were determined from the date of conception until the 13th week of gestation, second trimester from 14th week to the 28th week, and third trimester from the 29th weeks until birth. Entire pregnancy averages were calculated by using the period of conception as a reference start point until the newborn's delivery**.** All calculations and subsequent statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary NC, USA).

Statistical Analysis

Descriptive statistics and distributions were examined for the air pollution metrics and for the clinical and demographic variables. Excluded and included participants were compared to assess differences in population included in this study. Pearson correlation coefficients were calculated to assess the association between air pollution exposure windows, as well as within air pollutants. Metrics for the two air pollutants were used in separate logistic regression models to model the association with preterm birth. Logistic regression was used to estimate crude and adjusted odd ratios (ORs) and 95% confidence intervals (CIs) for the associations between preterm birth and each air pollutant estimated by all three exposure assessments methods for each of the four windows of interest (first, second, and third trimesters, as well for the entire pregnancy). Initially, single trimester exposure were included in the logistic regression models to describe the association between trimester-specific air pollution exposure metrics and preterm birth adjusted for covariates of interest. Potential confounders were chosen on the basis of biological plausibility (regardless of statistical significance).

Unadjusted models were fit to examine the air pollution metrics' association with preterm birth. Models adjusted for maternal age, parity, and infant sex were performed in order to examine differences in associations found when only covariates typically available from birth registries were available. A full model was fit that included covariates of interest as available from our study: -marital status, maternal education (years of education), smoking frequency, parity, mother's calf circumference, and infant sex. We also included an indicator variable for cohort in the model, to accommodate the different study aims and data collection protocols for each of the cohorts.

Effect estimates were standardized by calculating interquartile ranges (IQR) of exposure for each pollutant and windows of interest, and presenting OR's per IQR increase in each of the pollutants. Additionally, associations were examined across quartiles, using the lowest quartile as the reference concentration.

RESULTS

Figure III-1 shows the spatial distribution of study participants in the Mexico City Metropolitan Area and the monitors of the SIMAT air monitoring network. Of the 2,098 pregnant women with georeferenced data, 891 (42,4%) had complete information on covariates of interest and estimated PM_{10} and O_3 air pollution concentrations by different methods and windows (Table III-1). About 40% of the women in both the included and excluded groups were primiparous. 13.2% of the births were preterm in the included group compared with 53.2% in the excluded population. Women in the included population were similar in terms of marriage and education.

Average PM_{10} and O_3 pollution levels estimated by different methods were relatively similar for the different windows in pregnancy (Table III-3). As expected, Pearson correlation coefficients between trimesters and between exposures were moderate ($r=0.42 – 0.93$, all $p<0.001$). Correlations were less strong when comparing between methods during different trimesters (data not shown).

Relationships between air pollution metrics estimated by different exposure assessment and preterm birth were assessed using bivariate analysis, i.e., in unadjusted models (Tables III-4, III-5, and III-6). In most cases, the air pollution metrics were not significantly associated with preterm birth as individual predictors. In general, the vast majority of the trimester-specific and entire pregnancy air pollution exposures were not associated with preterm birth in the adjusted models. We next point out some of the associations that were observed in these regression analyses.

PM_{10} levels at the second quartile of exposure (41-58 $\mu g/m^3$) during the second trimester were associated with preterm birth when exposure was estimated by the citywide average method in the unadjusted model when compared against the reference category (OR=1.75, 95% CI: (1.00 – 3.05)) (Table III-4, Figure III-2). This association decreased when adjusting for covariates of interest. Also, the association was not present when examining other pollution exposure assessment methods. As higher quartiles of exposures were tested for the presence of associations, higher positive point estimates of effects were observed for the majority of the methods and pollutants. This was observed in adjusted models as well.

The second quartile of exposure to O_3 (70-80 ppb) was associated with an increase in risk of preterm birth during the first trimester of pregnancy when

examining adjusted associations (OR=1.94, 95% CI: (1.04-3.58), when compared to the reference category (Table III-5, Figure III-3). Moreover, the second quartile of exposure to O_3 during the entire pregnancy period had a statistically significant positive association (OR=1.76, 95% CI: (1.01 – 3.07)) when adjusted for the birth registry covariates, as well as when adjusting for full model covariates (OR=2.08, 95% CI: (1.07 – 4.08)), when compared to the reference category. Crude models did not reflect the same pattern as adjusted models.

When pollution was modeled continuously, we did not find statistically significant associations for PM_{10} and O_3. CWA models tended to have higher positive effect estimates than other interpolation methods. Adjusting for birth registry or full model covariates produced similar odds ratios to the other methods. Also, crude effect estimates for exposure during the entire pregnancy were attenuated and similar to the ones produced when adjusting for birth registry and full model covariates.

DISCUSSION AND CONCLUSION

This study describes the association between air pollution and preterm birth using several exposure assessment methods (citywide averaging, nearest monitor, and inverse distance weighting) to estimate individual level exposure in a Mexican cohort of pregnant women recruited from 1997 to 2004. Several researchers have studied the association that air pollutants have with preterm birth, but most of the evidence is insufficient and inconclusive as to whether the relationship exists (Sram, Binkova et al. 2005; Ritz and Wilhelm 2008; Woodruff, Parker et al. 2009). Our study adds to the body of research addressing this question.

We found that effect estimates during individual trimesters increased as the exposure assessment method incorporated spatial methods for PM_{10} exposure. Similarly, models that included full covariate information showed stronger effect estimates for the first, second, and third trimester of pregnancy. In our study, we found significant associations in the second quartile of PM_{10} exposure during the second trimester using the CWA method when compared with the reference category. This association was absent when the nearest monitor method was used to assess exposure, suggesting that limited local variation influenced by proximity to monitors does not produce the same effects as the other methods that use data from more sites in the available monitoring network.

A study that compared different exposure assessment methods, and the relationship that NO_2 has with birth weight, suggests that resulting exposure misclassification and bias introduced by methods that use all available air quality monitors may be prevented by incorporating proximity models or models that account for the area size (Lepeule, Caini et al. 2010). Moreover, temporally adjusted land-use-regression (LUR) models are capable of producing narrower confidence intervals with more precise effect estimates, but not necessarily larger effect estimates than spatial averaging using all available monitoring stations (Brauer, Lencar et al. 2008).

We did not find specific trends in exposure windows of major importance for preterm birth. Our ability to assess trimester specific effects in models that simultaneously included all three trimesters was limited since ambient monitoring based exposures were highly correlated across pregnancy windows, causing variance inflation (data not shown).

The strengths of this study lie in the use of georeferenced data developed for this cohort, since the cohort lacked such information originally, having questionnaire data to assess potential confounders of interest not typically available from birth registries, and the use of temporal and spatial data to estimate daily individual pollution concentrations which allow for a wide array of windows of exposure to be studied. Because many different approaches to assess individual exposure to air pollutants have been used in perinatal epidemiology research, heterogeneity in published findings has been attributed, in part, to this factor (Woodruff, Parker et al. 2009). Because we calculated several exposure metrics, from simple averages that do not require knowledge of participant residential location, to metrics that account for location, our results can be compared with a variety of published analyses.

Limitations in our work include small number of preterm cases, which limit the power to detect associations. This can be observed by the wide confidence intervals in the upper quartiles of exposure (Table III-4). Also, the lack of personal air pollution exposure information does not allow the validation of our models. However, it has been shown that levels of outdoor air pollution reflect indoor exposure levels in Mexico City (Rojas-Bracho 1994). Also, ambient monitors do not capture the range of exposure that pertains to different activity patterns that occur indoor and outdoor. Residual confounding resulting from risk factors that we could not control for (season, stress, anti-oxidant intake, etc) could bias this study.

Several mechanistic pathways have been proposed for how air pollutants such as PM_{10} and O_3 might influence risk of preterm birth. Inflammatory pathways and oxidative stress have previously been linked to air pollution (Kelly 2003; Chuang,

Chan et al. 2007; Latzin, Frey et al. 2011; van den Hooven, de Kluizenaar et al. 2012). Moreover, polycyclic aromatic hydrocarbon (PAH) may increase mutagenesis in cells, produce antiestrogenic effects, and help in the creation of DNA adducts increasing the susceptibility of the developing fetus (Bui, Tran et al. 1986; Perera, Jedrychowski et al. 1999).

In conclusion, this study provided evidence of an increase in risk for preterm birth among women exposed to ordinary levels of two key air pollutants in Mexico City. Overall, effect estimates showed null findings attributed to the exposure assessment challenges that individual estimation of air pollution from air monitoring data pose, and in part to the limited sample size of our population. It is also worth noting that classifying preterm birth dichotomously and using logistic regression models, may limit the power of detecting an increase in the probability of developing a premature birth compared to modeling gestational age as a continuous variable. Previous studies have assessed the association that environmental toxicants have with gestational instead of preterm birth (Cantonwine, Hu et al. 2010). In this analysis, we had a 41% power to detect a 1.20 fold increase in the odds of preterm birth for every standard deviation increase in exposure, so very limited.

Nonetheless, the significant findings that larger studies have had, and the mechanistic pathways by which air pollution influences health, suggest continuing to study the possibility of increased risk of preterm birth among women exposed to air pollution is an important endeavor that can yield knowledge relevant to prevention of preterm birth.

Figure III-1. Distribution of the air pollution monitoring network in Mexico City and residence location of women participants throughout Mexico City (1997-2004).

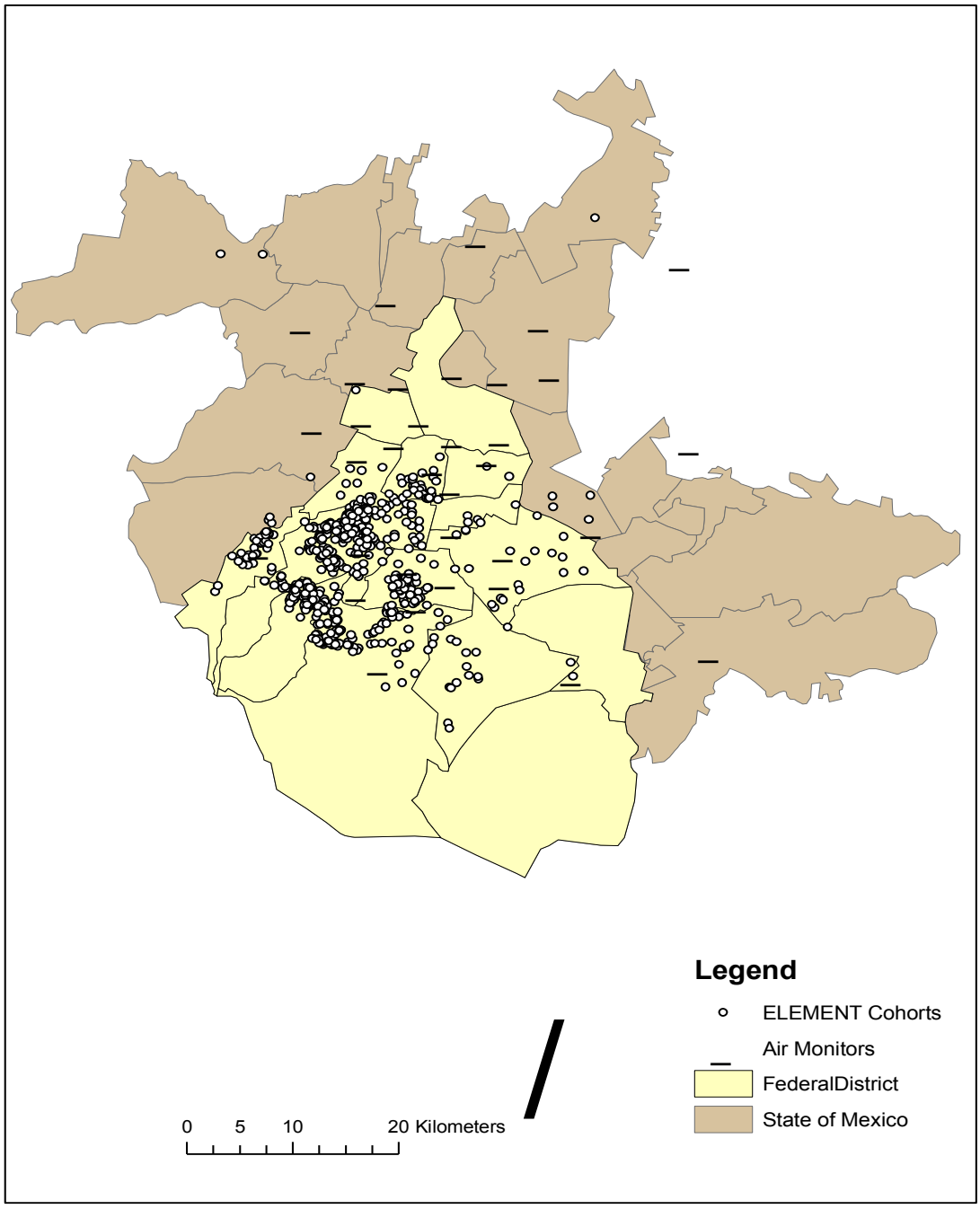

Figure III-2: Crude and adjusted odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth for the second quartile of exposure to PM_{10} estimated by the citywide average, nearest monitor, and inverse distance weighting methods during 2nd trimester .

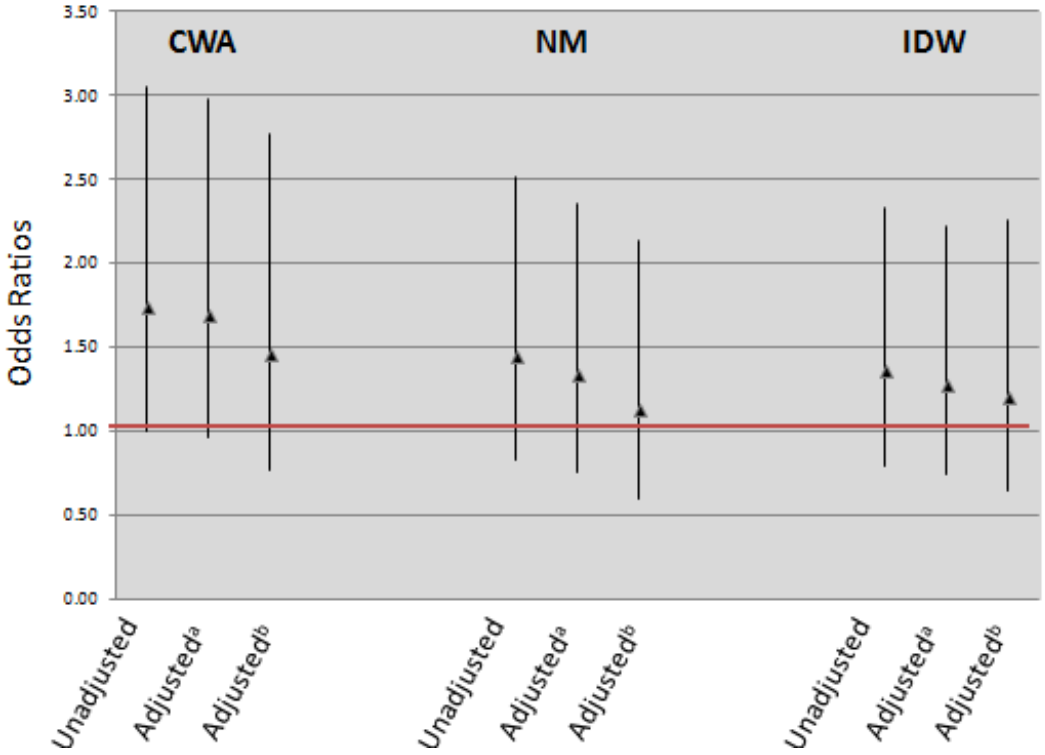

Figure III-3: Crude and adjusted odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth for the second quartile of exposure to PM_{10} estimated by the citywide average, nearest monitor, and inverse distance weighting methods during the entire pregnancy period .

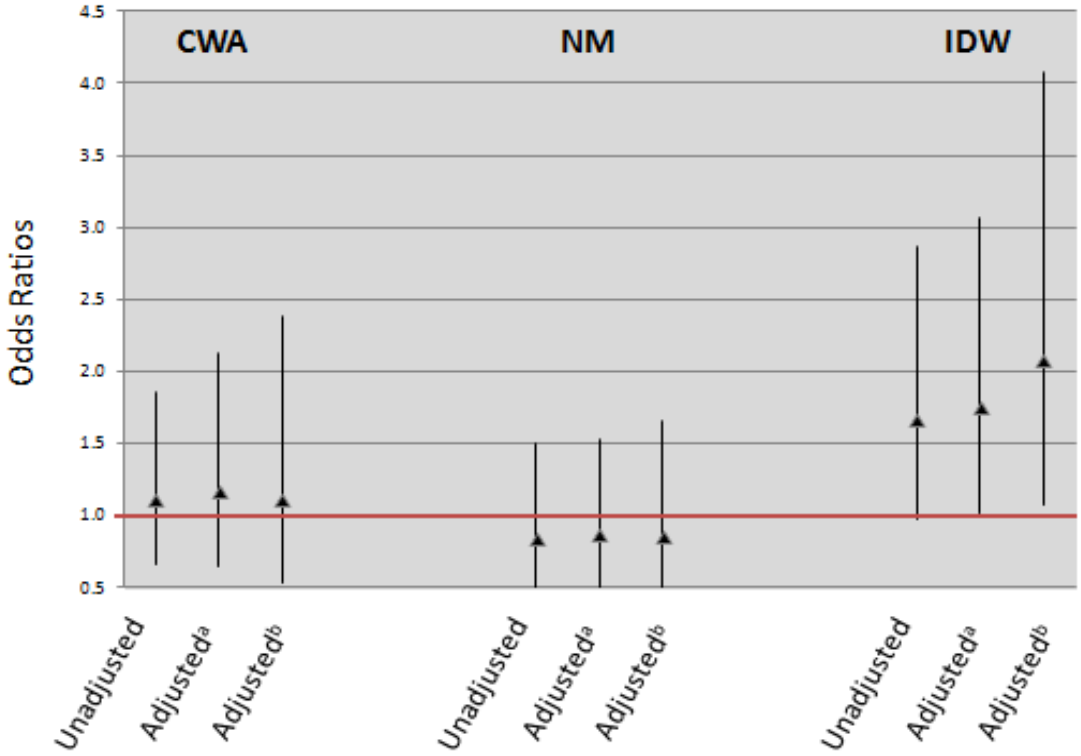

Table III-1. Characteristics of the study population of women in Mexico City (1997-2004).

Maternal Characteristics	Included		Excluded[a]		p-value
	n		n		
Total Population (%)	891		564		
Infant Sex					
Male (%)	450	49.5	202	36.8	0.15
Female(%)	441	50.5	166	29.4	
Missing (%)			196	34.8	
Age (years)					
<18 (%)	29	3.3	13	2.3	0.58
18-34 (%)	795	89.2	507	89.9	
>34 (%)	67	7.5	43	7.6	
Parity					
Nulliparous (%)	345	38.7	189	33.5	0.14
1-2 (%)	315	35.4	218	38.7	
≥3 (%)	231	25.9	157	27.8	
Marital Status					
Married (%)	642	72.0	392	30.1	0.36
Not Married (%)	249	28.0	169	69.9	
Education (years)					
<12 (%)	464	52.1	315	55.9	0.12
≥12 (%)	427	47.9	246	43.6	
Smoking					
No (%)	854	95.9	520	92.2	0.19
Yes (%)	37	4.1	15	2.7	
Missing			29	0.1	
Preterm Birth					
Yes (%)	118	86.8	264	46.8	<0.0001
No (%)	773	13.2	300	53.2	
Calf Circumference (cm)					
<32 (%)	166	18.6	46	8.2	0.65
32-34 (%)	211	23.7	65	11.5	
>34-36 (%)	299	33.6	85	15.0	
>36 (%)	215	24.1	48	8.5	
Missing (%)			320	56.7	
Calf Circumference (cm)	Mean(STD)	34.3(3.1)		34.0(3.2)	0.59
Cohort					
2-BL	343	38.5	118	20.9	<0.0001
2-PL	185	20.8	139	24.6	
3-SF	363	40.7	307	54.4	

[a]Excluded: Participants with missing data (i.e., pollution exposure metrics and covariates of interest). Preterm birth defined as births with <38 weeks of gestation.

Table III-2. Odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth from bivariate analysis with covariates of interest.

Maternal Characteristics	n	PTB OR(95%CI)
Infant Sex		
Female	449	REF
Male	442	0.94(0.56,1.59)
Maternal Age (yr)		
<18	29	REF
18-34	806	1.81(0.24,13.6)
>34	67	4.9(0.60,40.31)
Continuous	902	1.02(0.97,1.07)
Parity		
Nulliparous	351	REF
1-2	319	0.95(0.50,1.79)
≥3	232	1.33(0.71,2.52)
Continuous	902	1.19(0.94,1.52)
Marital Status		
Married	649	REF
Not Married	253	1.20(0.69,2.12)
Education	902	
<12	471	REF
≥12	431	0.77(0.45,1.30)
Continuous	902	0.94(0.86,1.03)
Smoking		
No	865	REF
Yes	37	1.26(0.30,5.36)
Continuous	902	0.97(0.75,1.27)
Calf Circumference (cm)		
<32	169	REF
32-34	301	0.95(0.43,2.13)
>34-36	214	1.11(0.48,2.57)
>36	218	1.52(0.69,3.36)
Continuous	902	1.05(0.96,1.14)

Table III-3. Descriptive statistics of air pollutant exposures during different periods of pregnancy for women in Mexico City (1997-2005)

	1st Trimester			2nd Trimester			3rd Trimester			Entire Pregnancy		
Pollutant	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR
PM10_CWA	57.4(17.4)	59.7	26.3	62.1(21.7)	61.7	30.1	59.8(16.3)	66.1	28.7	60.5(10.5)	58.8	21.0
PM10_NM	46.5(18.2)	44.0	26.0	50.5(21.0)	49.9	27.9	50.6(17.3)	54.1	25.0	50.0(12.3)	49.4	15.1
PM10_IDW	50.7(17.5)	49.6	24.6	55.1(21.2)	54.1	30.2	54.4(16.9)	58.0	29.9	54.3(11.6)	53.0	16.8
O3_CWA	78.1(12.1)	76.7	17.2	79.6(13.2)	81.3	25.3	79.4(13.7)	78.4	20.3	79.0(10.0)	77.3	17.5
O3_NM	87.4(18.3)	86.0	25.4	88.4(18.0)	88.1	28.0	87.5(17.0)	86.4	25.3	87.8(14.1)	87.4	21.6
O3_IDW	84.7(14.0)	83.7	19.9	86.1(15.0)	87.3	24.2	85.5(14.5)	84.8	20.9	85.4(11.5)	85.1	18.2

[a] Units are in $\mu g/m^3$ for PM_{10} and ppb for O_3. CWA=Citywide Average; NM=Nearest Monitor; IDW=Inverse Distance Weighting. SD=Standard deviation; IQR= interquantile range. N=902 for PM10; N=1474 for all other pollutants

Table III-4. Crude and adjusted odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth compared with the lowest exposure level of PM_{10} estimated by the citywide average, nearest monitor, and inverse distance weighting methods.

		Unadjusted[a]	Adjusted[b]	Adjusted[c]			Unadjusted[a]	Adjusted[b]	Adjusted[c]			Unadjusted[a]	Adjusted[b]	Adjusted[c]
Quartiles	N	OR%95CI	OR%95CI	OR%95CI	Quartiles	N	OR%95CI	OR%95CI	OR%95CI	Quartiles	N	OR%95CI	OR%95CI	OR%95CI
		Citywide Average Method					Nearest Monitor Method					Inverse Distance Weighting		
		First Trimester					**First Trimester**					**First Trimester**		
<41	222	REF	REF	REF	<32	224	REF	REF	REF	<36	225	REF	REF	REF
41 - 59	222	1.46 (0.84, 2.51)	1.32 (0.76, 2.30)	1.31 (0.71, 2.43)	32 - 44	226	1.34 (0.78, 2.29)	1.31 (0.76, 2.26)	1.25 (0.68, 2.31)	36 - 49	225	1.46 (0.87, 2.45)	1.41 (0.83, 2.39)	1.28 (0.70, 2.32)
59 - 68	223	1.31 (0.75, 2.72)	1.07 (0.60, 1.89)	1.15 (0.59, 2.25)	44 - 58	216	1.36 (0.79, 2.35)	1.17 (0.68, 2.05)	1.10 (0.60, 2.06)	49 - 60	218	0.96 (0.55, 1.67)	0.85 (0.48, 1.52)	0.97 (0.51, 1.85)
>68	224	0.86 (0.47, 1.56)	0.74 (0.39, 1.38)	0.85 (0.44, 1.67)	>58	225	0.79 (0.46, 1.44)	0.73 (0.40, 1.36)	0.72 (0.38, 1.39)	>60	223	0.74 (0.41, 1.33)	0.64 (0.35, 1.22)	0.63 (0.33, 1.22)
		Second Trimester					**Second Trimester**					**Second Trimester**		
<41	225	REF	REF	REF	<32	226	REF	REF	REF	<35	226	REF	REF	REF
41 - 58	223	1.75 (1.00, 3.05)	1.70 (0.96, 2.98)	1.46 (0.77, 2.77)	32 -44	223	1.45 (0.83, 2.52)	1.34 (0.76, 2.35)	1.13 (0.60, 2.14)	35 - 49	219	1.36 (0.79, 2.33)	1.28 (0.74, 2.22)	1.21 (0.65, 2.26)
58-67	224	1.41 (0.79, 2.51)	1.24 (0.69, 2.23)	1.06 (0.55, 2.05)	44 - 59	219	1.53 (0.88, 2.65)	1.37 (0.78, 2.41)	1.02 (0.54, 1.93)	49 - 62	223	1.32 (0.77, 2.28)	1.11 (0.64, 1.95)	0.90 (0.47, 1.72)
>67	219	1.24 (0.69, 2.23)	1.07 (0.56, 2.00)	1.00 (0.51, 1.96)	>59	223	0.97 (0.54, 1.76)	0.87 (0.46, 1.64)	0.78 (0.41, 1.51)	>62	223	0.84 (0.47, 1.52)	0.73 (0.38, 1.38)	0.67 (0.34, 1.30)
		Third Trimester					**Third Trimester**					**Third Trimester**		
<39	221	REF	REF	REF	<33	225	REF	REF	REF	<35	224	REF	REF	REF
39 - 58	223	0.75 (0.43, 1.31)	0.66 (0.37, 1.16)	0.68 (0.35, 1.33)	33 - 44	224	0.72 (0.42, 1.23)	0.74 (0.43, 1.27)	0.63 (0.33, 1.20)	35 - 49	225	0.78 (0.45, 1.36)	0.77 (0.44, 1.35)	0.73 (0.38, 1.42)
58 - 69	224	0.81 (0.47, 1.40)	0.82 (0.47, 1.43)	0.89 (0.46, 1.70)	44 - 61	217	0.68 (0.40, 1.18)	0.75 (0.43, 1.32)	0.70 (0.37, 1.32)	49 - 66	220	1.02 (0.60, 1.73)	1.11 (0.64, 1.91)	1.08 (0.58, 2.01)
>69	223	1.06 (0.63, 1.79)	1.23 (0.69, 2.20)	1.21 (0.65, 2.24)	>61	225	0.81 (0.48, 1.36)	0.99 (0.55, 1.80)	0.91 (0.48, 1.71)	>66	222	0.87 (0.50, 1.49)	1.08 (0.58, 2.00)	1.01 (0.52, 1.95)
		Entire Pregnancy					**Entire Pregnancy**					**Entire Pregnancy**		
<49	226	REF	REF	REF	<40	225	REF	REF	REF	<43	225	REF	REF	REF
49 - 55	223	1.03 (0.64, 1.64)	0.96 (0.60, 1.54)	0.78 (0.45, 1.38)	40 - 45	225	0.73 (0.44, 1.23)	0.68 (0.37, 1.23)	0.34 (0.16, 0.72)	43 - 50	226	1.23 (0.73, 2.06)	1.24 (0.70, 2.19)	0.96 (0.46, 1.98)
55 - 60	224	0.77 (0.47, 1.28)	0.69 (0.39, 1.22)	0.66 (0.36, 1.22)	45 - 53	225	0.60 (0.35, 1.02)	0.46 (0.24, 0.90)	0.23 (0.10, 0.51)	50 - 56	223	0.83 (0.47, 1.44)	0.72 (0.36, 1.47)	0.53 (0.23, 1.22)
>60	218	1.56 (0.61, 4.05)	0.82 (0.28, 2.39)	0.86 (0.29, 2.55)	>53	216	0.60 (0.35, 1.03)	0.45 (0.22, 0.93)	0.26 (0.11, 0.56)	>56	217	0.78 (0.44, 1.38)	0.63 (0.29, 1.37)	0.49 (0.20, 1.18)

[a] Unadjusted model; [b] Model adjusted by infant sex, maternal age, parity, and cohort; [c] Model adjusted by infant sex, maternal age, cohort, calf circumference, and smoking during pregnancy

Table III-5. Crude and adjusted odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth compared with the lowest exposure level of O_3 estimated by the citywide average, nearest monitor, and inverse distance weighting method.

		Unadjusted[a]	Adjusted[b]	Adjusted[c]			Unadjusted[a]	Adjusted[b]	Adjusted[c]			Unadjusted[a]	Adjusted[b]	Adjusted[c]
Quartiles	N	OR%95CI	OR%95CI	OR%95CI	Quartiles	N	OR%95CI	OR%95CI	OR%95CI	Quartiles	N	OR%95CI	OR%95CI	OR%95CI
		Citywide Average Method					Nearest Monitor Method					Inverse Distance Weighting		
		First Trimester					**First Trimester**					**First Trimester**		
<62	220	REF	REF	REF	<70	222	REF	REF	REF	<69	222	REF	REF	REF
62-72	225	0.94 (0.56,1.59)	0.84 (0.50, 1.44)	1.16 (0.63, 2.13)	70-80	223	1.38 (0.81, 2.34)	1.46 (0.84, 2.50)	1.94 (1.04, 3.58)	69-77	223	1.07 (0.63, 1.79)	1.09 (0.64, 1.83)	1.15 (0.63, 2.11)
72 -79	223	0.92 (0.54, 1.55)	0.80 (0.47, 1.38)	0.91 (0.49, 1.71)	80-90	224	0.83 (0.47, 1.49)	0.83 (0.46, 1.49)	0.93 (0.46, 1.88)	77-86	223	0.82 (0.48, 1.41)	0.82 (0.47, 1.42)	0.91 (0.49, 1.70)
>79	223	0.62 (0.35, 1.10)	0.57 (0.31, 1.04)	0.67 (0.34, 1.31)	>90	222	1.04 (0.60, 1.82)	1.06 (0.60, 1.90)	1.16 (0.60, 2.24)	>86	223	0.63 (0.35 1.11)	0.59 (0.32, 1.07)	0.66 (0.34, 1.26)
		Second Trimester					**Second Trimester**					**Second Trimester**		
<62	221	REF	REF	REF	<70	222	REF	REF	REF	<69	223	REF	REF	REF
62-72	224	1.19 (0.69, 2.02	1.08 (0.63, 1.86)	1.13 (0.61, 2.12)	70-80	224	1.07 (0.62, 1.84)	1.09 (0.62, 1.90)	1.34 (0.71, 2.54)	69-77	222	1.05 (0.60, 1.81)	1.03 (0.59, 1.81)	1.23 (0.65, 2.36)
72 -81	223	0.99 (0.57, 1.72)	0.84 (0.47, 1.51)	0.73 (0.37, 1.46)	80-90	222	1.08 (0.62, 1.87)	1.01 (0.57, 1.75)	1.12 (0.58, 2.17)	77-86	223	1.24 (0.73, 2.12)	1.08 (0.62, 1.89)	1.17 (0.61, 2.28)
>81	223	0.87 (0.49, 1.54)	0.77 (0.41, 1.42)	0.79 (0.39, 1.52)	>90	223	0.92 (0.52, 1.60)	0.85 (0.46, 1.55)	0.92 (0.46, 1.82)	>86	223	0.81 (0.45, 1.44)	0.76 (0.42, 1.42)	0.85 (0.42, 1.71)
		Third Trimester					**Third Trimester**					**Third Trimester**		
<62	222	REF	REF	REF	<70	222	REF	REF	REF	<69	222	REF	REF	REF
62-72	223	1.25 (0.72, 2.17)	1.41 (0.80, 2.47)	1.31 (0.66, 2.58)	70-80	223	0.74 (0.42, 1.31)	0.84 (0.46, 1.51)	0.92 (0.46, 1.83)	69-77	223	0.92 (0.59, 1.60)	1.01 (0.57, 1.81)	0.98 (0.49, 1.96)
72 -81	223	1.04 (0.59, 1.82)	1.19 (0.64, 2.19)	1.07 (0.53, 2.18)	80-90	225	1.10 (0.64, 1.85)	1.24 (0.70, 2.16)	1.36, (0.70, 2.64)	77-88	223	0.96 (0.55, 1.66)	1.15 (0.62, 2.11)	1.13 (0.55, 2.31)
>81	223	1.12 (0.64, 1.96)	1.53 (0.77, 3.06)	1.35 (0.64, 2.87)	>90	221	0.93 (0.54, 1.61)	1.07 (0.57, 2.02)	1.11 (0.55, 2.25)	>88	223	1.03 (0.60, 1.77)	1.32 (0.69, 2.55)	1.27 (0.60, 2.70)
		Entire Pregnancy					**Entire Pregnancy**					**Entire Pregnancy**		
<68	222	REF	REF	REF	<72	223	REF	REF	REF	<72	222	REF	REF	REF
68-72	223	1.11 (0.66, 1.86)	1.17 (0.64, 2.12)	1.11 (0.52, 2.38)	72-80	222	0.85 (0.48, 1.50)	0.87 (0.49, 1.53)	0.86 (0.44, 1.66)	72-77	223	1.67 (0.97, 2.86)	1.76 (1.01, 3.07	2.08 (1.07, 4.08)
72 -76	223	0.89 (0.52, 1.53)	0.74 (0.35, 1.59)	0.73 (0.29, 1.78)	80-88	223	1.28 (0.76, 2.16)	1.33 (0.77, 2.28)	1.33 (0.72, 2.46)	77-83	223	1.13 (0.64, 2.01)	1.18 (0.63, 2.22)	1.11 (0.52, 2.37)
>76	223	0.65 (0.37, 1.16)	0.46 (0.21, 1.05)	0.41 (0.16, 1.06)	>88	223	0.81 (0.46, 1.43)	0.79 (0.42, 1.48)	0.71 (0.35, 1.41)	>83	223	1.04 (0.58, 1.87)	0.97 (0.48, 1.93)	1.11 (0.51, 2.41)

[a] Unadjusted model; [b] Model adjusted by infant sex, maternal age, parity, and cohort; [c] Model adjusted by infant sex, maternal age, cohort, calf circumference, and smoking during pregnancy

Table III-6. Odds ratios (OR's) and 95% confidence intervals (CI's) for risk of preterm birth per interquartile range increase in air pollution in Mexico City (1994-2004), using three different exposure metrics.

			Model 1[a]	Model 2[b]	Model 3[c]
			First Trimester		
Pollutant	Method	IQR	OR (95% CI)	OR (95% CI)	OR (95% CI)
PM_{10} ($\mu g/m^3$)	CWA	26.41	0.89 (0.65, 1.23)	0.79 (0.56, 1.12)	0.81 (0.56, 1.18)
	NM	26.41	0.85 (0.62, 1.14)	0.79 (0.57, 1.09)	0.80 (0.57, 1.12)
	IDW	24.69	0.85 (0.63, 1.15)	0.78 (0.56, 1.07)	0.79 (0.56, 1.11)
O_3 (ppb)	CWA	15.81	0.76 (0.55, 1.07)	0.73 (0.51, 1.04)	0.75 (0.51, 1.09)
	NM	19.97	0.93 (0.72, 1.20)	0.91 (0.70, 1.19)	0.90 (0.68, 1.21)
	IDW	16.11	0.81 (0.61, 1.07)	0.79 (0.59, 1.05)	0.82 (0.60, 1.12)
			Second Trimester		
PM_{10} ($\mu g/m^3$)	CWA	25.92	1.10 (0.78, 1.54)	0.97 (0.67, 1.39)	0.94 (0.63, 1.40)
	NM	26.91	0.99 (0.72, 1.36)	0.93 (0.66, 1.31)	0.87 (0.60, 1.25)
	IDW	26.40	0.98 (0.70, 1.37)	0.90 (0.62, 1.30)	0.85 (0.57, 1.26)
O_3 (ppb)	CWA	18.21	0.90 (0.64, 1.28)	0.82 (0.56, 1.22)	0.80 (0.52, 1.23)
	NM	20.44	0.95 (0.73, 1.23)	0.90 (0.68, 1.19)	0.92 (0.68, 1.24)
	IDW	17.88	0.92 (0.69, 1.23)	0.86 (0.63, 1.17)	0.88 (0.62, 1.24)
			Third Trimester		
PM_{10} ($\mu g/m^3$)	CWA	30.12	1.11 (0.78, 1.58)	1.13 (0.79, 1.63)	1.16 (0.78, 1.72)
	NM	27.96	0.92 (0.67, 1.27)	1.02 (0.71, 1.45)	0.98 (0.67, 1.43)
	IDW	30.71	0.97 (0.68, 1.39)	1.07 (0.71, 1.60)	1.03 (0.67, 1.59)
O_3 (ppb)	CWA	18.37	1.05 (0.74, 1.49)	1.28 (0.82, 1.99)	1.18 (0.73, 1.91)
	NM	19.97	0.96 (0.74, 1.25)	1.00 (0.74, 1.35)	0.98 (0.71, 1.32)
	IDW	18.24	1.02 (0.76, 1.37)	1.12 (0.79, 1.61)	1.07 (0.73, 1.58)
			Entire Pregnancy		
PM_{10} ($\mu g/m^3$)	CWA	10.05	1.04 (0.81, 1.33)	0.91 (0.67, 1.22)	0.92 (0.67, 1.26)
	NM	12.34	0.87 (0.67, 1.13)	0.83 (0.60, 1.13)	0.78 (0.54, 1.09)
	IDW	12.93	0.87 (0.65, 1.17)	0.75 (0.50, 1.13)	0.70 (0.44, 1.09)
O_3 (ppb)	CWA	8.06	0.85 (0.65, 1.11)	0.75 (0.51, 1.48)	0.67 (0.42, 1.07)
	NM	16.56	0.91 (0.68, 1.21)	0.91 (0.68, 1.21)	0.87 (0.61, 1.25)
	IDW	11.25	0.87 (0.66, 1.14)	0.81 (0.58, 1.13)	0.81 (0.55, 1.17)

[a] Unadjusted model; [b] Model adjusted by infant sex, maternal age, parity, and cohort; [c] Model adjusted by infant sex, maternal age, cohort, calf circumference, and smoking during pregnancy. CWA=Citiwide Average; NM=Nearest Monitor IDW=Inverse Distance Weigihting

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CHAPTER IV

AIR POLLUTION AND PRETERM BIRTH IN MEXICO CITY, MEXICO: EFFECT MODIFICATION BY BONE LEAD

INTRODUCTION

The rapid demographic and industrial growth that Mexico City has experienced in the last decades has been reflected in the environmental problems experienced in the metropolitan area. During 1985, the government began efforts to reduce lead in gasoline and ultimately by 1991 lead had been phased out of all the gasoline sold in the metropolitan area (Driscoll, Mushak et al. 1992). Other main sources of lead exposure include paints, glazed-ceramic pottery, and traces of lead that are present in air from industrial or other emission sources. Environmental lead exposure has been a problem for the general population in Mexico City, especially susceptible populations such as children, pregnant women, and the elderly (Romieu, Palazuelos et al. 1994). Moreover, lead exposure has been associated with female reproductive outcomes and certain susceptible windows in pregnancy that are crucial for the developing fetus have been implicated as the exposure periods of concern (Andrews, Savitz et al. 1994; Tellez-Rojo, Hernandez-Avila et al. 2004; Cantonwine, Hu et al. 2010).

There are two main routes, inhalation and ingestion, through which individuals are exposed to lead,. Both routes aid on the absorption of the contaminant which is

sequestered primarily by red blood cells (Smith, Osterloh et al. 1996). The fraction of lead that has been thought to be biologically available to the developing fetus is present in blood plasma. Thus, the use of whole blood lead concentrations as a proxy for acute exposures may not represent exposures that may affect pregnancy due to its short half-life (Smith, Ilustre et al. 1998; Tellez-Rojo, Hernandez-Avila et al. 2004; Popovic, McNeill et al. 2005). During pregnancy, bone demineralization occurs at a more rapid rate allowing for the release of lead into circulation, thus contributing to the body burden of lead from bone reservoirs (Silbergeld 1991; Gulson, Jameson et al. 1997; Riess and Halm 2007). Bone lead levels measurable in the patella and tibia represent accumulation over years to decades and thus represent a biomarker of a chronic exposure that becomes more bio-available during pregnancy. This potential route of exposure and the presence of high levels of air pollutants simultaneously in Mexico City may present a risk for developing infants during critical stages in pregnancy.

Outdoor air pollution and its constituents have been shown to be a problem for megacities in the developing world, especially Mexico City with its rapidly growing population. Outdoor air pollutants have been associated with different reproductive health outcomes such as intrauterine growth restriction (IUGR) (Maisonet, Correa et al. 2004; van den Hooven, Pierik et al. 2011), low birth weight (LBW) (Wilhelm and Ritz 2003; Salam, Millstein et al. 2005; Bell, Ebisu et al. 2007), and preterm birth (Huynh, Woodruff et al. 2006; Llop, Ballester et al. 2010; Chang, Reich et al. 2012; Le, Batterman et al. 2012).

Recent interest in perinatal health outcomes (e.g. preterm birth rates) has sparked new scientific research, as well as recognition from governmental entities and the scientific community on the importance of identifying and learning more about how environmental toxicants may influence the onset of preterm birth. Although associations found between environmental exposures and preterm birth are not consistent in their findings, four areas of interest for further research have been agreed upon: (1) confounding and effect modification, (2) spatial and temporal exposure variations, (3) vulnerable windows of exposure, and (4) multiple pollutants (Woodruff, Parker et al. 2009).

Outdoor air pollution and lead exposure have been found to independently affect preterm birth. Lead and air pollution exposures have been shown to activate oxidative stress pathways that can increase biomarkers during pregnancy (Stohs and Bagchi 1995; Kelly 2003). If this mechanism is affected this could lead to the early onset of parturition causing a premature delivery. The objective of this study is to examine whether cumulative lead exposure, as measured in tibia and patella, modifies the association between two key air pollutants, particulate matter less than ten microns in aerodynamic diameter (PM_{10}) and ozone (O_3), and preterm birth.

METHODS:

Study Population

The study population was recruited at three different hospitals in Mexico City during 1997 to 2005 as part of the ELEMENT (Early Life Exposure in Mexico to Environmental Toxicants) study (http://sitemaker.umich.edu/merg/element) (Gonzalez-Cossio, Peterson et al. 1997; Tellez-Rojo, Hernandez-Avila et al. 2004;

Lamadrid-Figueroa, Tellez-Rojo et al. 2007). Participants attending these hospitals are from a low to moderate income population and lived in Mexico City metropolitan area during the time of their participation in the study. All cohort participants signed an informed consent before enrolling in the study. The research protocols were approved by the Ethics and Research Committee or Institutional Review Boards of the National Institute of Public Health (Cuernavaca, Mexico City), the Harvard School of Public Health, the Brigham and Women's Hospital, the University of California, and participating hospitals. The present analysis was approved by the University of Michigan.

Exclusion criteria for the cohorts included risk factors related to calcium metabolism, medical conditions that could cause low birth weight (<2500g), a physician's diagnosis of multiple fetuses, preeclampsia, kidney, psychiatric or cardiac conditions, gestational diabetes, history of repeated urinary infections, and seizure conditions that would require medication (Tellez-Rojo, Hernandez-Avila et al. 2004; Hu, Tellez-Rojo et al. 2006; Lamadrid-Figueroa, Tellez-Rojo et al. 2007).

For the present study, gestational age was determined by the mother's recall of her last menstrual period (LMP) since ultrasound information was not collected at participating hospitals. Using the estimated gestational age and the infant's date of birth, the infant's date of conception was calculated. Preterm birth was defined as live births occurring before 38 weeks of gestation. Other variables determined *a priori* to be of interest as potential confounders of the preterm and air pollution association were derived from questionnaire data. These included maternal age, smoking

frequency, educational attainment, marital status, infant sex, and parity. These variables have been associated with preterm birth in previous studies Additionally, calf circumference, measured during the 10 month post-partum visit to the clinics, was used to estimate maternal nutritional status during pregnancy. Although other variables, such as body mass index, have been used for this purpose, calf circumference was the variable available for the majority of the cohort participants. The residences of the women included in this study all were assigned geographical coordinates using methods described previously (Chapter III), to enable estimation of air pollution exposure according to the assumption that women spend most of their time in the region of the city where they live.

Air Pollution Exposure Metrics

Hourly air pollution data (PM_{10} and O_3) reported by the automated air pollution monitoring network in Mexico City were downloaded from 1994-2004. Although the network measures concentrations of three other gaseous pollutants, PM_{10} and O_3 were chosen because they are the two pollutants that most frequently exceed health-based standards in Mexico City and because they exhibit strong spatial gradients across the metropolitan area, enhancing contrasts in estimated exposure when residence location is taken into consideration. Daily 24-hour averages for PM_{10} were calculated when at least 75% of the hourly data was reported for the contaminant. Daily averages for O_3 were produced by utilizing the 8-hour maximum running average, which corresponds to the regulatory standard, using the same rule for missing hours as for PM_{10}.

Three different exposure assessment methods were developed to estimate daily individual exposure to outdoor air pollution using the air monitoring network data: 1)

citywide average (CWA); 2) nearest monitor (NM); 3) inverse distance weighting (IDW). The CWA method utilizes data from all available reporting monitors to calculate a weighted average, the NM method utilizes the closest monitor, determined by distance, to the participant's residence to assign individual exposure, and the IDW method bases its predictions on a weighted average in which weights are inversely proportional to the square of the distance from the mother's residence to the air pollution monitor. Daily air pollution exposure metrics produced by each method were used to calculate concentrations during trimester-specific critical windows of exposure during pregnancy.

Exposure Window Calculation

Air pollution concentration averages were created for the entire period of pregnancy, and first, second, and third trimesters. First trimester periods were defined from the date of conception until the 13th week of gestation, second trimester from 14th week to the 28th week, and third trimester from the 29th weeks until birth. Entire pregnancy averages were calculated by using the period of conception as a reference start point until the newborn's delivery**.** All calculations and subsequent statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary NC, USA).

Maternal Bone Lead Measurements

Participant's bone lead levels were measured using a spot-source ^{109} Cd K-XRF instrument, at two places in the bones, the mid-tibial shaft and the patella, during an approximately one-month postpartum visit to the clinic. Physical principles and method specifications have been described in detail elsewhere (Burger, 1990). Concentrations with uncertainty levels higher than 10 and 15 μg/g for tibia and patella

lead were excluded from the analysis, as it has been done in similar analysis using bone lead measurements (Park, O'Neill et al. 2008; Cantonwine, Hu et al. 2010).

Statistical Analysis

Descriptive statistics and distributions were examined for the lead biomarkers (lead concentrations in patella and tibia), air pollution metrics (PM_{10} and O_3), and for the socio-demographic variables. Pearson correlation coefficients were calculated to compare the three exposure biomarkers. We used t-test and analysis of variance (ANOVA) to evaluate differences among socio-demographic variable categories and biomarker lead concentrations. For modeling purposes, separate data sets were created to include the individuals with air pollutant metrics by exposure assessment method and windows of interest, as well as having available data related to the covariates of interest. Four data sets were created for each pollutant/lead biomarker combination: (1) PM_{10} and patella lead levels; (2) PM_{10} and tibia lead levels; (3) O_3 and patella lead levels; and lastly (4) O_3 and tibia lead levels. To evaluate potential socio-demographic difference between excluded and included individuals, p-values were calculated using t-test or ANOVA.

To examine effect measure-modification, two exposure categories (high and low exposure) were created for each biomarker. The medians were used to establish the cut points for lead concentrations in patella and tibia.

Logistic regression models were used to evaluate the association between the PM_{10} and O_3 exposure metrics and preterm birth by biomarker exposure category, with and without adjustment for covariates. Odds ratios from logistic models were determined per interquartile range (IQR) increase in air pollutants. Odds ratios were

produced for all three exposure assessments methods for each of the four windows of interest (first, second, and third trimesters, as well for the entire pregnancy).

Then, datasets were stratified by the high and low levels of the biomarkers to yield stratum-specific OR's and confidence intervals. Our qualitative criterion for the presence of effect-measure modification was that the confidence interval for the low stratum did not enclose the point estimate of the OR for the high stratum. Interaction terms were based on continuous measures of patella and tibia lead concentrations. Other possible interactions between individual covariates of interest and bone lead were assessed.

The following covariates were included: maternal age, parity, and infant sex. We also included an indicator variable for cohort in the model, to accommodate the different study aims and data collection protocols for each of the cohorts. Although we identified other covariates that were of interest for this study, in order to have statistical power, we limited the regression models to fewer covariates of interest. This follows a rule of thumb suggestion for logistic regression that no more than one independent variable be included per every ten preterm cases in the population (Wilson VanVoorhis and Morgan 2007). However, because more covariates than we could use in the regression models were available for the study population, we present the descriptive statistics on those.

RESULTS

The initial sample available was 2,098 individuals. Our population consisted of 856 (41%) pregnant women who had complete information on socio-demographic variables by different exposure methods, pregnancy windows, and bone lead

measurements, for PM_{10} and O_3 exposure concentrations respectively (Table IV-1). Table IV-1 shows the included and excluded populations for the patella analysis. The included group had a higher preterm birth prevalence (9.1%) compared with 8.0% in the excluded population. Calf circumference in the included population were significantly higher than in the excluded population. Other socio-demographic characteristics were not different between groups.

Table IV-2 shows median concentrations for each lead exposure biomarker by maternal socio-demographic characteristics. Overall, bone lead levels did not vary significantly by socio-demographic groups. Patella and tibia levels were significantly different when examining maternal age. Women with more than one child also had higher lead levels (p-0.06). Significant differences were observed for mother's calf circumference categories. As expected, older women had higher levels of lead in patella and tibia, since exposure to airborne lead decreased after the 1997 gasoline phase-out.

Air pollution metrics are shown in Table IV-3. Average PM_{10} concentrations were relatively similar among trimesters. Different exposure methods produced similar means and standard deviations for PM_{10}. In contrast, O_3 means reported by CWA for each trimester and the entire pregnancy period were significantly lower than those reported by NM and IDW. The NM method produced higher exposures and standard deviations than the IDW method.

Correlations between bone lead biomarkers show patella and tibia lead levels were moderately correlated (r=0.36) (Data not shown). Median bone lead levels for the were 8.1μg/g for patella and 7.7μg/g for tibia. We found no significant associations for

bone lead biomarkers, as a continuous or categorical predictor variable, in bivariate analyses with preterm birth (Table IV-4).

The covariate-adjusted associations of air pollution with preterm birth across dichotomous categories of bone lead are presented in Table IV-5 and Table IV-6. Single multiplicative interaction term between bone lead and air pollution were assessed (Table IV-5 and Table IV-6). Neither patella nor tibia lead level significantly modified the associations of PM_{10} exposure and preterm birth, for all methods and windows. Similarly, bone lead levels did not modify the associations of O_3 with preterm birth (Table IV-6). Although all associations with air pollution were not significant, the highest point estimates of the OR's for preterm birth were generally seen for third-trimester air pollution exposures with the exception of the O_3 exposure metrics. Second trimester exposures had effect estimates that were lower than those observed for other windows of susceptibility.

DISCUSSION AND CONCLUSION

Additionally, we did not find strong evidence of a variation in the risk of preterm birth associated with PM_{10} or O_3 exposures when stratifying the population by lead concentration categories in patella or tibia. Of the total of three positive, significant associations between pollution (O_3) and preterm birth in lead-exposure stratified analyses, two of these were among the women with lower tibia lead, and one among the women with high patella lead. Although no particular trend was found among exposure methods or pregnancy windows, we noticed consistent increases in the point estimates for the OR's for preterm birth across all exposure methods for third-trimester exposures. Before putting our findings in context of other related

research, we mention strengths and limitations of our work. This is the first perinatal epidemiology study that we know of in Mexico City using several different exposure assessment approaches for both air pollution and lead.

In the absence of quality-controlled and electronically available birth registry data from Mexico City, we combined data from three previously conducted studies to allow us to take a first look at how lead and air pollution together might impact birth outcomes in Mexico City. Because the aim of those previous studies was mainly to assess how lead exposure among pregnant women could impact the health and development of their babies, the population sample and number of preterm cases were low, restricting our power to look at the association of interest. Further, gestational age was not ultrasound confirmed. However, among the strengths of this population, geo-referencing of the women allowed us to evaluate spatial as well as temporal aspects of air pollution exposure. Also, the few findings that were significant associations were in the expected direction (that is, higher odds of preterm birth among women more highly exposed to pollution).

Previous research on main effects of lead exposure and birth outcomes has had mixed results. Cantonwine et al. (2010) studied the relationship of lead biomarkers and gestational age and premature delivery in a subset population of the Mexican cohort and found negative associations between blood lead and preterm, but not with bone lead. Another study that related bone lead with birthweight found that tibia lead was the only biomarker related with birth weight (Gonzalez-Cossio, Peterson et al. 1997). Clearly the complex interaction between bone and blood lead and the uncertainties in exposure classification for an entire pregnancy when just one or a few blood samples

during pregnancy, and one bone-scan post-partum, are available, may play a role in these mixed results.

In terms of comparing associations across exposure metrics, here again sample size limits the ability to draw strong conclusions given the wide confidence intervals. In another study, employment of land-use-regression models (LUR) showed small confidence intervals when compared with area monitoring data and also showed smaller effect estimates considering the spatial resolution and possible reduction of exposure misclassification (Brauer, Lencar et al. 2008).

In spite of the overall null findings of the present study, evaluating environmental co-exposures and how they may influence pregnancy outcomes remains of critical interest. Lead and air pollution in particular may act through a common mechanistic pathway to affect birth outcomes. Evidence suggests that exposure to air pollutants such as PM_{10} and O_3 can impact the production of inflammatory responses and oxidative stress (Gomaa, Hu et al. 2002; Kelly 2003; Perera, Tang et al. 2005; Alfaro-Moreno, Ponce-de-Leon et al. 2007). Similarly, chronic lead exposure has been linked to production of oxidative stress (Grassi, Tell et al. 2007). Increase in inflammatory cytokines has been suggested as a pathway for early labor onset. Moreover, generation of free radicals by activated inflammatory cells also contributes to oxidative stress which can affect the duration of pregnancy. Although there is a need for further clarification of the pathways involved, previous evidence that smoking increases preterm risk, and tobacco smoke has constituents in common with outdoor air pollution, strengthens the biological plausibility of the possible association.

This study provided some evidence that a mother's cumulative lifetime exposure to lead may modify the association between O_3 concentrations and risk of preterm birth, but because of sample size limitations in the present study and the paucity of similar research, definitive conclusions on the interaction of these environmental toxicants on birth outcomes are not possible at this time. The fact that effect estimates tended to be highest for pollution exposures occurring during third trimester of pregnancy, a stage of pregnancy when bone resorption is at its highest, suggests future research evaluating critical windows of exposure is warranted.

Table IV-1. Characteristics of the study population of women in Mexico City (1997-2004).

Maternal Characteristics	Included	%	Excluded[a]	%	p-value
	n		n		
Total Population (%)	856	100	599	100	
Infant Sex					0.69
Male (%)	440	51.4	212	35.4	
Female(%)	416	48.6	191	31.9	
Missing (%)			196	32.7	
Age (years)					0.23
<18 (%)	30	3.5	12	2.0	
18-34 (%)	763	89.1	539	90.0	
>34 (%)	63	7.4	47	7.8	
Parity					0.21
Nulliparous (%)	330	38.6	204	34.0	
1-2 (%)	303	35.4	230	38.4	
≥3 (%)	223	26.0	165	27.6	
Marital Status					0.45
Married (%)	616	72.0	418	69.8	
Not Married (%)	240	28.0	178	29.7	
Missing (%)			3		
Education (years)					0.19
<12 (%)	446	52.2	333	55.6	
≥12 (%)	408	47.8	265	44.2	
Smoking					
No (%)	802	95.7	572	95.4	0.1200
Yes (%)	36	4.3	16	2.7	
Missing(%)			11	1.8	
Preterm Birth					<0.0001
Yes (%)	111	13.0	271	45.2	
No (%)	745	87.0	328	54.8	
Missing (%)			11	1.8	
Calf Circumference (cm)					0.55
<32 (%)	168	19.6	44	7.3	
32-34 (%)	207	24.2	69	11.5	
>34-36 (%)	285	33.3	99	16.5	
>36 (%)	196	22.9	67	11.2	
Missing (%)			320	53.4	
Calf Circumference (cm)	Mean(STD)	34.2(3.2)		34.5(3.0)	0.24
Cohort					<0.0001
2-BL	360	42.1	101	16.9	
2-PL	181	21.1	143	23.9	
3-SF	315	36.8	355	59.3	

[a]Excluded: Participants with missing data (i.e., pollution exposure metrics and covariates of interest). Preterm birth defined as births with <38 weeks of gestation.

Table IV-2. Median lead biomarkers by socio-demographic variables for women and their infants participating in Mexico City-based cohort studies, 1997-2004.

Maternal Characteristics	n	Lead level biomarkers: Patella (μg/g)	*p*-value	n	Tibia (μg/g)	*p*-value
Total	856	8.1		671	7.7	
Infant Sex			0.1463			0.30
Male	440	7.9		335	7.4	
Female	416	8.4		336	7.8	
Missing						
Maternal Age (years)			<0.0001			0.01
<18	30	0.87		22	1.4	
18-34	769	8.0		600	7.7	
>34	63	11.7		49	10.4	
Parity			<0.0001			0.06
Nulliparous	330	5.9		256	6.6	
1-2	303	9.1		238	9.0	
≥3	223	9.8		177	7.8	
Marital Status			0.0854			0.67
Married	616	8.4		488	7.7	
Not Married	240	7.4		183	7.6	
Education (years)			0.9912			0.99
<12	446	8.1		353	7.6	
≥12	408	8.1		316	7.7	
Smoking			0.4868			0.13
No	802	8.2		33	7.5	
Yes	36	8.9		623	10.5	
Preterm[a]			0.2034			0.22
Yes	111	9.1		82	8.0	
No	745	8.0		589	7.7	
Calf Circumference (cm)						
<32	168	8.0	<0.0001	138	7.8	0.002
32-34	207	8.2		158	7.1	
>34-36	285	8.3		230	8.2	
>36	196	8.0		145	7.8	
Cohort			<0.0001			<0.0001
2-BL	360	7.9		349	7.7	
2-PL	181	12.0		154	12.3	
3-SF	315	6.2		168	5.2	

[a]Preterm birth defined as births with <38 weeks of gestation.

P-value for the difference among the socio-demographic variable categories.

Table IV-3. Descriptive statistics of air pollutants exposures during different periods of pregnancy for women in Mexico City (1997-2004); n = 856 for PM_{10} and O_3.

	1st Trimester			2nd Trimester			3rd Trimester			Entire Pregnancy		
Pollutant	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR	Mean(SD)[a]	Median[a]	IQR
PM10_CWA	57.4(17.4)	59.7	26.3	62.1(21.7)	61.7	30.1	59.8(16.3)	66.1	28.7	60.5(10.5)	58.8	21.0
PM10_NM	46.5(18.2)	44.0	26.0	50.5(21.0)	49.9	27.9	50.6(17.3)	54.1	25.0	50.0(12.3)	49.4	15.1
PM10_IDW	50.7(17.5)	49.6	24.6	55.1(21.2)	54.1	30.2	54.4(16.9)	58.0	29.9	54.3(11.6)	53.0	16.8
O3_CWA	78.1(12.1)	76.7	17.2	79.6(13.2)	81.3	25.3	79.4(13.7)	78.4	20.3	79.0(10.0)	77.3	17.5
O3_NM	87.4(18.3)	86.0	25.4	88.4(18.0)	88.1	28.0	87.5(17.0)	86.4	25.3	87.8(14.1)	87.4	21.6
O3_IDW	84.7(14.0)	83.7	19.9	86.1(15.0)	87.3	24.2	85.5(14.5)	84.8	20.9	85.4(11.5)	85.1	18.2

[a] Units are in $\mu g/m^3$ for PM_{10} and ppb for O_3. CWA=Citywide Average; NM=Nearest Monitor; IDW=Inverse Distance Weighting. SD=Standard deviation; IQR= interquantile range. N=902 for PM10; N=1474 for all other pollutants

Table IV-4. Bivariate analysis showing odds ratios (OR's) and 95% confidence intervals (CI) of preterm birth by bone lead levels, for women in Mexico City, 1997-2004. Associations with continuous bone lead are expressed per one unit increase in bone lead.

Lead Biomarkers	n	PTB OR (95%CI)
Patella Lead µg/g		
≤10	831	REF
>10	831	0.96(0.64,1.43)
Continuous	1,662	1.00(0.98,1.02)
Tibia Lead µg/g		
≤9	713	REF
>9	716	1.05(0.68,1.66)
Continuous	1,429	1.01(0.98,1.03)

PTB: Preterm is defined as any delivery <37 weeks of gestation

Table IV-5. Estimated odds ratios (OR's) and 95% confidence intervals (CI's) for preterm birth per interquartile range increase in PM_{10} by tibia and patella lead category.

		Patella Pb			Tibia Pb		
Method	Window of Exposure	≤ Median (n=423)	> Median (n=423)	p-value for interaction	≤ Median (n=333)	> Median (n=333)	p-value for interaction
		OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	
CWA	1st Trimester	1.28 (0.62, 2.60)	0.74 (0.36, 1.53)	0.53	1.31(0.58,2.95)	0.55(0.23,1.36)	0.88
	2nd Trimester	0.81 (0.36, 1.84)	0.54 (0.27, 1.08)	0.76	0.42(0.17,1.04)	0.65(0.27,1.54)	0.37
	3rd Trimester	1.36 (0.58, 3.20)	1.19 (0.64, 2.22)	0.36	1.90(0.76,4.80)	1.73(0.82,3.65)	0.45
	Entire Pregnancy	1.42 (0.68, 3.01)	0.71 (0.43, 1.18)	0.23	1.04(0.51,2.12)	0.82(0.44,1.54)	0.29
NM	1st Trimester	1.10 (0.54, 2.26)	0.76 (0.41, 1.41)	0.67	0.94(0.42,2.10)	0.59(0.27,1.31)	0.61
	2nd Trimester	0.63 (0.27, 1.48)	0.60 (0.31, 1.16)	0.90	0.33(0.13,0.86)	0.81(0.38,1.70)	0.15
	3rd Trimester	1.08 (0.48, 2.41)	0.98 (0.52, 1.86)	0.42	1.20(0.51,2.84)	1.55(0.69,3.47)	0.81
	Entire Pregnancy	0.88 (0.43, 1.80)	0.61 (0.33, 1.14)	0.36	0.44(0.17,1.14)	0.71(0.34,1.49)	0.16
IDW	1st Trimester	1.13 (0.56, 2.28)	0.69 (0.35, 1.33)	0.46	1.03(0.47,2.24)	0.53(0.23,1.23)	0.91
	2nd Trimester	0.66 (0.27, 1.59)	0.55 (0.27, 1.14)	0.72	0.30(0.12,0.80)	0.77(0.33,1.80)	0.17
	3rd Trimester	1.29 (0.49, 3.36)	1.16 (0.58, 2.29)	0.28	1.37(0.52,3.62)	1.99(0.83,4.77)	0.46
	Entire Pregnancy	1.01 (0.38, 2.68)	0.54 (0.25, 1.13)	0.26	0.42(0.14,1.25)	0.74(0.31,1.75)	0.20

All models adjusted for maternal age, parity, infant sex, and cohort. Medians for patella and tibia were 8.1 µg/g and 7.7 µg/g, respectively. CWA=citywide average; NM= nearest monitor; IDW=inverse distance weighting

Table IV-6. Estimated odds ratios (OR's) and 95% confidence intervals (CI's) for preterm birth per interquartile range increase in O_3 by tibia and patella category.

		Patella Pb			Tibia Pb		
Method	Window of Exposure	≤ Median (n=689)	> Median (n=688)	p-value for interaction	≤ Median (n=612)	> Median (n=612)	p-value for interaction
		OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	
CWA	1st Trimester	1.19 (0.59, 2.41)	0.85 (0.42, 1.74)	0.41	1.37(0.59,3.16)	0.60(0.24,1.47)	0.29
	2nd Trimester	0.73 (0.32, 1.71)	0.55 (0.25, 1.21)	0.58	0.33(0.12,0.89)	0.40(0.14,1.10)	0.97
	3rd Trimester	1.13 (0.45, 2.82)	1.70 (0.75, 3.85)	0.74	1.54(0.54,4.33)	1.90(0.67,5.44)	0.85
	Entire Pregnancy	1.05 (0.46, 2.41)	0.68 (0.31, 1.50)	0.25	0.62(0.22,1.76)	0.28(0.08,0.92)	0.33
NM	1st Trimester	1.00 (0.56, 1.78)	1.10 (0.66, 1.83)	0.56	1.47(0.77,2.80)	0.82(0.45,1.51)	0.24
	2nd Trimester	0.64 (0.34, 1.22)	0.77 (0.47, 1.24)	0.40	0.57(0.30,1.09)	0.64(0.35,1.17)	0.92
	3rd Trimester	0.98 (0.50, 1.95)	1.07 (0.61, 1.86)	0.99	1.20(0.57,2.52)	1.29(0.64,2.63)	0.80
	Entire Pregnancy	0.77 (0.36, 1.64)	0.89 (0.49, 1.62)	0.58	0.96(0.42,2.20)	0.72(0.36,1.44)	0.48
IDW	1st Trimester	1.09 (0.58, 2.04)	1.05 (0.61, 1.80)	0.92	1.52(0.78,2.98)	0.76(0.39,1.47)	0.17
	2nd Trimester	0.79 (0.38, 1.64)	0.68 (0.38, 1.21)	0.76	0.50(0.23,1.09)	0.54(0.26,1.13)	0.93
	3rd Trimester	1.21 (0.56, 2.56)	1.25 (0.64, 2.41)	0.55	1.56(0.64,3.78)	1.58(0.68,3.70)	0.71
	Entire Pregnancy	1.04 (0.47, 2.30)	0.84 (0.46, 1.54)	0.52	1.06(0.43,2.60)	0.62(0.29,1.34)	0.29

All models adjusted for maternal age, parity, infant sex, and cohort. Medians for patella and tibia were 8.1 µg/g and 7.7 µg/g, respectively. CWA=citywide average; NM= nearest monitor; IDW=inverse distance weighting

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CHAPTER V

CONCLUSIONS

This dissertation has developed and compared air pollution exposure assessment methods for estimating individual exposure to air pollutants in Mexico City during the calendar year of 2008 in 1,000 simulated individuals. It has used three of the exposure assessment methods to estimate exposure to air pollutants in a cohort of pregnant women recruited from 1994 to 2004 to investigate the association that preterm birth has with PM_{10} and O_3. Lastly, making use of information regarding chronic exposure to lead, measured in tibia and patella, in the same population, we examined whether variation in levels of tibia and patella lead modify the association of air pollution and preterm birth. This chapter provides a summary of the findings, as well as recommendations and future research directions.

CHAPTER II CONCLUSIONS

In chapter two, we found that the four exposure assessment methods yielded similar, but not identical, results for the air pollutants examined. In addition, the ranges of exposure metrics produced by the methods that incorporated geo-referenced location data of individuals were significantly higher in comparison to estimates produced by the CWA approach. High correlation coefficients between OK and IDW suggest that these two interpolation methods were similarly able to predict spatial gradients in concentrations of air pollutants. As far as we know this is the first study to

examine differences in air pollution exposure metrics produced by commonly used exposure assessment methods in Mexico City.

Overall, our findings suggest that residential location can enhance perinatal epidemiology studies by incorporating temporal and spatial components of air pollution that are not seen by more simple methods like spatial averaging. Also, ordinary kriging produced very similar exposure metrics when compared with inverse distance weighting.

In order to improve exposure assessment in epidemiological studies looking at air pollution and preterm birth, geostatistical interpolation methods that use air pollution monitoring network data can be employed. Moreover, temporal and spatial data, as well as activity patterns of individuals will help to avoid exposure misclassification which could bias the studied association. Nevertheless, one must recognize that air pollution methods have their limitations, such as the need to evaluate exposure at the personal level.

Future areas of research include the development of automated statistical packages that can help estimate daily variogram parameters with more ease. Variogram estimation is very complex, especially when all air pollution monitors do not report data at all times (Liao, Peuquet et al. 2006). Also, inclusion of methods that combined geographical information systems, meteorological data, and geostatistics could improve the estimates developed for individual estimation of air pollutants (Pearce, Rathbun et al. 2009).

CONCLUSIONS CHAPTER III

In chapter three we assessed the association between air pollution and preterm birth using several exposure assessment methods (citywide averaging, nearest monitor, and inverse distance weighting) to estimate individual level exposure. Overall, this study did not provide evidence of an increase in risk for preterm birth among women exposed to higher levels of two key pollutants in Mexico City. We attribute these null findings in part to the exposure assessment challenges that individual estimation of air pollution from air monitoring data pose, and in part to the limited sample size of our population. We did find that effect estimates during individual trimesters increased as the exposure assessment method incorporated spatial methods for PM_{10} exposure. Also, we did not find specific trends in exposure windows of major importance for preterm birth.

Future directions involve the identification of specific windows of exposure, establishment of longitudinal studies that can delineate the influence of different biological pathways in the development of premature labor, assessment of non-linearity in associations with environmental toxicants, incorporation of time-activity patterns which could help in avoiding exposure misclassification of affected individuals, and the examination of the relationship that other criteria air pollutants may have with preterm birth (Huynh, Woodruff et al. 2006; Ritz, Wilhelm et al. 2007; Ritz and Wilhelm 2008).

CONCLUSION CHAPTER IV

Among the metals, lead exposure has been extensively studied and associations have been found for different windows of pregnancy in relation to the onset of preterm

birth (Andrews, Savitz et al. 1994; Ettinger, Tellez-Rojo et al. 2004; Cantonwine, Hu et al. 2010). Our analysis did not find strong evidence of a variation in the risk of preterm birth associated with PM_{10} or O_3 exposures, by lead concentration categories in patella or tibia.

Future research should be directed at studying different lead biomarkers that have been used in previous literature, such as plasma and whole blood lead, as well as designing studies that can confirm previous findings (Smith, Hernandez-Avila et al. 2002; Lamadrid-Figueroa, Tellez-Rojo et al. 2006). This could lead to the development of strategies that can help prevent the mobilization of lead from bone during conditions of rapid bone turnover such as pregnancy and lactation (Ettinger, Tellez-Rojo et al. 2006).

Evaluating how multiple environmental toxicants can influence the development of a baby and his/her future life course is important because pregnant women are exposed to a mixture of contaminants in air, food, water and other media. Just as calcium supplementation of the mother can reduce exposure of a developing fetus to lead, intake of foods rich in anti-oxidant vitamins may also mitigate harmful effects of air pollution. However, the ultimate preventive strategy may be to reduce environmental contamination, and interventions such as phasing lead out of gasoline and seeking cleaner modes of transport and manufacturing can reduce the burden pollution places on our health.

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