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Los Angeles

Effects of air pollution on pregnancy outcomes in Los Angeles County

A dissertation submitted in partial satisfaction of the

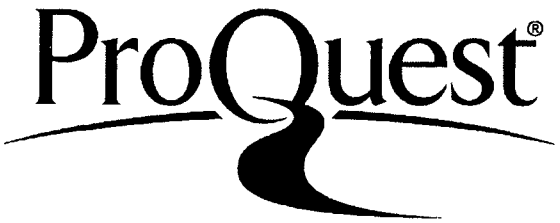
requirements for the degree Doctor of Philosophy

in Epidemiology

by

Jo Kay Chan Ghosh

2011



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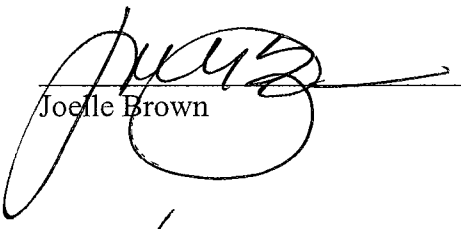

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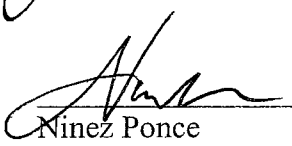

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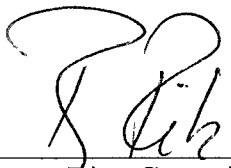

Beate Ritz, Committee Chair

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LIST OF ABBREVIATIONS

BAP: benzo(a)pyrene

BGP: benzo(g,h,i)perylene

BTEX: benzene, toluene, ethyl benzene, and xylenes

CARB: California Air Resources Board

CMB: Chemical Mass Balance

CI: Confidence interval

CO: carbon monoxide

EC: elemental carbon

ETS: environmental tobacco smoke

GIS: Geographic Information Systems

IQR: Inter-quartile range

IAQ: indoor air quality

IUGR: intrauterine growth restriction

LA: Los Angeles

LBW: low birth weight

LUR: land use-based regression

MATES III: Multiple Air Toxics Exposure Study III

NO: nitric oxide

NO_2: nitrogen dioxide

NO_x: nitrogen oxides

O_3: ozone

OC: organic carbon

OR: odds ratio

PAHs: polycyclic aromatic hydrocarbons

$PM_{2.5}$: particulate matter <2.5 μm in aerodynamic diameter

PM_{10}: particulate matter <10 μm in aerodynamic diameter

SCAQMD: South Coast Air Quality Management District

SES: socioeconomic status

UFP: ultrafine particles; particles <0.1 μm in aerodynamic diameter

U.S. EPA: United States Environmental Protection Agency

VOCs: volatile organic compounds

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ABSTRACT OF THE DISSERTATION

Effects of air pollution on pregnancy outcomes in Los Angeles County

by

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Background. Prenatal exposure to air pollution has been associated with increased risk of adverse birth outcomes, and traffic exhaust is the most important contributor to air pollution in Los Angeles (LA) County, California. The majority of studies have used ambient "criteria pollutant" data (e.g. carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), and particulate matter less than 10 or 2.5 μm in aerodynamic diameter (PM_{10}, $PM_{2.5}$)), because these pollutants are measured at government-run air monitoring stations for regulatory purposes. These studies have some important limitations: (1) the sparse networks of monitoring stations may result in exposure misclassification for people who do not live close to a station; (2) the criteria pollutants may serve as imperfect markers of traffic exhaust pollution, and the actual causative agents could be air toxics such as polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), or certain metals found in traffic exhaust; and (3) these ambient measures do not capture exposures to poor indoor air quality, which may be significant for pregnant women, who, on average, spend over 15 hours/day in indoor

spaces. These studies serve to address some of these limitations of criteria pollutant studies of adverse birth outcomes.

Methods. Our studies focused on preterm birth (<37 weeks completed gestation), very preterm birth (<32 weeks completed gestation) and term low birth weight (LBW) (≥37 weeks completed gestation, and <2500g at birth) as the pregnancy outcomes of interest. We used several novel approaches to exposure modeling in these studies. First, we used ambient air toxics and criteria pollutant monitoring data from the California Air Resources Board (CARB), which runs a network of 4 air toxics monitors in LA County, California. Second, we used a land use-based regression (LUR) model that estimates NO, NO_2, and NO_x levels on a 20 meter x 20 meter grid across the entire county. LUR models use data from intensive monitoring of air pollutants over short periods of time, and also incorporate data on traffic counts, land use, greenness and brightness to create maps of air pollution across a geographical area. Third, we used survey measures of contributors to indoor air quality to assess exposures to key components of poor indoor air that could contribute to these adverse birth outcomes, including environmental tobacco smoke (ETS), and VOCs from personal and household products.

The first two studies used birth certificate data to identify singleton births from 1995-2006, and we restricted the study to those mothers who resided within 5 miles of a CARB air toxics station. We used the air toxics and LUR data to estimate air pollution exposures in each trimester of pregnancy, in the last pregnancy month, and across the entire pregnancy. The LUR model estimates were based on the geocoded location of the mother's residence at birth, and we also seasonalized these estimates using CARB station

data for NO, NO_2, and NO_x to create exposure averages for the specific pregnancy periods of interest. The study of term LBW compared cases to non-cases (full-term normal weight infants), while the study of preterm and very preterm birth used a case-control approach with incidence density sampling of controls matched on gestational age. Logistic regression and conditional logistic regression models were used to examine air pollution associations with term LBW and preterm/very preterm birth, respectively. The study of indoor air quality is based on the UCLA Environment and Pregnancy Outcomes Study (EPOS), which is nested case-control study of term LBW and preterm cases along with term normal-weight controls sampled from LA County mothers who delivered a baby in the year 2003. For the women who completed the EPOS survey, we used logistic regression to examine effect estimates of several measures of indoor air quality, incorporating survey measures of ETS exposure at home, residential use of nail polish, hairspray, and insect spray, and window ventilation.

Summary of findings. The LA County populations in our studies are predominantly Hispanic, multiparous, and of a lower-SES profile. Unseasonalized LUR estimates of ambient NO, NO_2, and NO_x exposures were associated with increased odds of term LBW, preterm birth, and very preterm birth. For term LBW, the strongest associations for seasonalized LUR-estimated and air toxics exposures were seen for the third trimester, the entire pregnancy, and the last pregnancy month averages. Third trimester benzene, toluene, ethyl benzene, and xylene exposures were associated with term LBW when stratified by closest monitoring station. Exposure to PAHs (benzo(a)pyrene and benzo(g,h,i)perylene) were associated with increased term LBW odds in the last

pregnancy month. Vanadium exposures were not associated with increased term LBW risk. These results are consistent with previous studies of term LBW using criteria pollutant data, which also observed associations with entire pregnancy and late pregnancy exposures to air pollution.

For preterm birth, we observed increased risk with seasonalized LUR-estimated exposures in the first trimester, last pregnancy month, and entire pregnancy averages, as well as entire pregnancy average exposure for benzene, toluene, ethyl benzene, and xylene (BTEX). When restricting to women who lived within 5 miles of the North Long Beach air toxics station, we observed increased odds of preterm birth with unseasonalized LUR, seasonalized LUR (first trimester, entire pregnancy), and entire pregnancy average PAHs and benzene. We also observed stronger associations between air pollution and preterm birth among African American mothers, compared to Hispanic and non-Hispanic white mothers, particularly for the seasonalized LUR and BTEX exposures. Odds of very preterm birth increased with higher exposures to seasonalized and unseasonalized LUR-estimated NO, NO_2, and NO_x, and BTEX pollutants for 1st trimester, 2nd trimester, entire pregnancy, and last month of pregnancy averages. PAH exposure also increased odds of very preterm birth, for last pregnancy month exposures. Vanadium was not associated with preterm birth or very preterm birth.

While unseasonalized LUR estimates reflect comparisons of air pollution levels across geographical areas (i.e. "spatial comparisons"), the analyses stratified by station or restricted to a single station effectively restrict the comparisons to temporal fluctuations in air pollution rather than spatial comparisons, which are more susceptible to confounding bias by socio-economic status (SES). By using both types of comparisons

in the same study, we are able to provide stronger evidence of the presence of a true effect. The stronger associations observed for women living near the North Long Beach station may be attributable to a more toxic pollutant mix due to port-related activities near that station, including shipping emissions and diesel truck exhaust.

Poor indoor air quality was also associated with increased odds of term LBW and preterm birth. Most notably, mothers who reported living with one or more smokers had increased odds of both adverse birth outcomes, although the risk was attenuated for those women who also reported keeping their windows open at least half the day. Additionally, women who reported using 1 or more of the surveyed personal and household products (nail polish, hairspray, and insect spray) regularly or frequently had increased odds of term LBW and preterm birth, but only if they also reported having low/no window ventilation. Mothers who worked at home exclusively during pregnancy had stronger associations with the ETS and personal/household product exposure measures, compared to women who reported working outside the home for at least some part of their pregnancy. Measures of home air quality are most likely better measures of exposure for at-home mothers compared to mothers who work outside the home due to the presumed length of time spent indoors at home.

These studies of air pollution and birth outcomes using air toxics data, LUR models, and indoor air quality exposure measures illustrate how exposure data sources beyond ambient criteria pollutants and newer exposure modeling methods can help address some key limitations of previous studies. Our analyses contribute to the existing evidence and help to identify causative agents and inform both policy decisions and

personal choices that will mitigate exposures to air pollution, particularly among pregnant women.

Chapter 1
Introduction and Methods

Background and Objectives

Summary of hypothesized links between air pollution and birth outcomes

In the past twenty years, epidemiologic studies have linked prenatal air pollution exposure to a variety of adverse birth outcomes, including low birth weight, small for gestational age, preterm birth, and cardiac birth defects[1-4]. Links between prenatal exposure to carbon monoxide (CO), particles (TSP, PM_{10}, $PM_{2.5}$), and polycyclic aromatic hydrocarbons (PAHs) and intrauterine growth restriction and/or preterm birth point to toxins in motor vehicle exhaust as possible causative agents.[2,5,6]

The majority of the studies used ambient (outdoor) criteria air pollutants to assess exposures mostly based on residential address.[7,8] However, there are some more recent studies employing land use-based regression (LUR) methods to model prenatal air pollution exposures,[9-14] including 2 recent studies conducted by our research group.[15,16] Additionally, a small number of studies measured exposures to polycyclic organic matter (POM)[17] and PAHs.[18,19], and reported negative impacts on a variety of fetal growth metrics. While traffic-related air pollution is the focus of most of these studies (which are primarily conducted in metropolitan areas), other sources of air pollution may be important in some populations. Studies have reported reductions in birth weight to be associated with prenatal exposure to coal burning[20], industrial petrochemical emissions[21], and coal mining activities[22]. Additionally, studies of residential biomass fuel burning in

developing nations have found large increases in the risk of low birthweight (LBW) in households using biomass fuels compared to households with cleaner burning fuels.[23-25] Environmental tobacco smoke is a known risk factor for many adverse pregnancy outcomes, and has been associated with decreased head circumference, decreases in birth weight, and increased risk of term LBW,[26,27] although studies of preterm birth are less consistent.[26,28,29]

Pregnancy constitutes a period of human development particularly susceptible to toxins because of high cell proliferation, organ development, and the changing capabilities of fetal metabolism.[30] The potential effects of prenatal exposure to air pollutants are dependent on the timing of exposure.[7] For low birth weight, the first and third trimesters are likely critical time windows, while prior studies of preterm birth have not been consistent in identifying critical windows of exposure although some studies suggest the first trimester and last month of pregnancy as sensitive periods.[7,31] Clearly, it is important to account for seasonal variations in addition to assessing spatial heterogeneity of outdoor air pollutants.

The biological mechanisms by which air pollution causes these adverse birth outcomes are unknown, although there are some hypothesized pathways. PAHs can cross into the placenta and disrupt placental perfusion leading to intrauterine growth restriction (IUGR)[32-40], or induce a pro-inflammatory cytokine response through the production of cytotoxic reactive oxygen species (ROS), which may initiate early parturition.[41-45] As summarized by Perera et al.,[46] current hypotheses on PAH mechanisms include anti-estrogenic effects,[47] binding of constituents to the human aryl hydrocarbon receptor to induce P450 enyzmes,[48] and DNA damage resulting in activation of apoptotic

pathways.[40,49,50] An alternative hypothesis is that air pollution may increase anti-inflammatory cytokines in the lower genital tract, increasing the risk for infection and subsequent inflammation, which could lead to preterm birth.[51]

Challenges to modeling air pollution exposures in pregnancy

There are many challenges in estimating air pollution exposure in population-based studies, especially when medium- or longer-term exposures are of interest, as is the case for pregnancy outcomes. Here, we discuss some of the main challenges relating to exposure modeling.

Temporal and spatial variation

Air pollution varies both spatially and temporally. Spatial variation is dependent on the location of sources of air pollution (e.g. freeways, industrial sources), the specific pollutant (e.g. NO vs ozone), as well as wind direction, and geographical features (e.g. valleys). Temporal variation is due to a variety of meteorological factors, including temperature, sunlight, humidity, and wind speed and direction. In Los Angeles, the predominant temporal pattern is to see high levels of ozone in the summer months, when sunlight causes NO_2 to react with oxygen in the air and form ozone. In contrast, winter months exhibit high levels of NO_x because of the lack of sunlight to break down these gases. In our air toxics data, PAHs, PM, and VOCs (benzene, toluene, ethyl benzene, and xylene (BTEX)) all peak in the winter months, while vanadium (a metal) peaks in the summer months.

Networks of government air monitoring stations provide detailed data on temporal variation of air pollutants, but have somewhat limited spatial coverage. Only 18 CARB

air monitoring stations provide data for the Los Angeles County metropolitan areas. Exposures based on monitoring station data are unlikely to be valid for people living far from the station. Therefore, previous studies have defined inclusion in the study based on residential addresses or zipcodes located within a fixed radius from the stations (e.g. 2-3 miles).[52,53]

A newer method used to characterize fine spatial variations in air pollution is land use-based regression (LUR) modeling. In this modeling approach, outdoor pollution measurements taken at locations throughout an urban area are related to Geographic Information System (GIS) predictors of traffic exhaust concentrations (such as traffic, roadway, household and population density).[54-57] The developed regression model is then used to predict exposures for large groups of subjects at residential locations based on knowledge of the GIS parameters at these locations. These models have been shown to have good predictive capability.[57,58] Typically, LUR models are based on NO_x measurements, which are relatively easy and cost-effective to measure. The additional information from traffic maps, land use data, greenness and brightness data help fine-tune the model to represent outdoor traffic-related pollution exposures.[31]

Pollution exposure mix, multiple pollutants and correlated data

Although epidemiological studies have associated traffic exhaust pollutants with adverse birth outcomes, these studies are not able to identify whether a pollutant is acting as a marker for traffic exhaust or whether it is the causative agent. Because air pollution is a mixture of gases, particles, and air toxics, which are often correlated due to common sources, it is difficult to identify any one causal agent within the mix of pollutants. In the

Los Angeles County region, traffic is a major source of these air pollutants, but industrial sources and indoor sources (e.g. smoking, use of cosmetic or household products containing VOCs) can have important influences on an individual's exposure. Multipollutant models can be used to disentangle effects of the different air pollutants, and have been recommended to be included in epidemiologic studies of air pollution.[59]

Study Objectives

The overall objective of this dissertation is to study the effects of air pollution on pregnancy outcomes in Los Angeles County. We chose to focus on preterm birth (<37 weeks completed gestation), very preterm birth (<32 weeks completed gestation) and term LBW (≥37 weeks completed gestation, and <2,500g at birth) as the pregnancy outcomes of interest. In particular, we employed three distinct exposure assessment methods and/or data sources. First, we used data on air toxics and criteria air pollutants to study the effects of prenatal exposure to regional traffic-related ambient air pollution. Second, we used LUR modeled estimates of NO, NO_2 and NO_x, which we additionally "seasonalized" to account for seasonal variations in air pollution; such LUR models represent local exposures to traffic-related ambient air pollution. Third, we examined the effects of indoor air quality on preterm birth and IUGR. By employing several air pollution exposure models to populations in the same region, we can develop a better understanding of the components and sources of air pollution that may be important to these health outcomes. Such information is important to inform policies regarding vehicle emissions controls and zoning regulations (e.g. the proximity of residential neighborhoods to freeways).

Study Populations and Methods

Study populations

The Air Toxics Study Birth Cohort (Birth Certificate Data)

This dataset includes births between 1/1/1995 to 12/31/2006 to women residing in Los Angeles County, California. These births and corresponding addresses were identified using electronic birth certificate data from the State of California. We excluded records with an address that could not be geocoded, or those which could only be geocoded to the county level centroid or poorer quality. Because we are using data from the four California Air Resources Board (CARB) air toxics monitoring stations (North Long Beach, Burbank, Downtown LA, and Azusa), we restricted the dataset to women who resided within 5 miles (≤5 miles) of one or more of these stations. Additionally, we excluded births with recorded abnormalities or defects, missing or extreme gestational ages (<140 days, or >320 days), missing or extreme birth weights (<500 g, or >5,000 g), and multiple gestations. After these exclusions, the cohort contained n=415,531 births over the 12 year period. This cohort, excluding preterm births, was used in the analysis of term LBW (n=379,103 total). For the preterm birth analysis, we selected all preterm cases from this cohort, and employed a risk-set sampling approach of controls, matching on gestational age. Ten controls will be selected for each case. This case-control dataset included 36,428 preterm cases and 364,280 matched controls. The dataset used to evaluate very preterm birth risk is a subset of the preterm birth case-control dataset, and included 3,463 cases and 34,630 matched controls.

The birth certificates provided data on gestational age and birth weight, which we used for the outcome definitions. The birth certificates also provided other variables that

may be important confounders in our study, such as maternal age, race/ethnicity, education, birthplace, parity, baby's sex, timing of prenatal care initiation, and prenatal care payment source.

The EPOS Study

The UCLA Environment and Pregnancy Outcomes Study (EPOS) is a case-control study nested within the year 2003 birth cohort of all women who resided in select zip codes of LA County [60]. The primary goal of EPOS was to study the effects of ambient air pollution on adverse birth outcomes. We used California State and LA County electronic birth certificate records to select live singleton births to mothers residing in zip codes near air pollution monitoring stations and/or major roadways. We included all cases of preterm birth (<37 weeks completed gestation) and low birthweight (<2,500g) from zip codes located near air monitoring stations, and a random sample of 30% of cases from the remainder of the selected zip codes. Controls (full term, normal weight babies) were matched to cases based on birth month, month that data were received from the county health department, and zip code set, for a total sample of 6,374 women. We reached and enrolled 2,543 of these women (40% response rate) approximately 3-6 months after delivery, including 1,028 cases of preterm birth, 233 cases of term LBW, and 1,282 controls.

Mothers were interviewed in English or Spanish by telephone, by mail survey, and during home visits. Information about maternal age, race/ethnicity, education, birthplace, parity, baby's sex, timing of prenatal care initiation, and prenatal care payment source, was obtained from birth certificates. The EPOS survey questionnaire

provided detailed information on factors affecting indoor air quality (e.g. household characteristics, including home type and frequency of window ventilation, use of VOC-containing personal and household products, and whether the woman lived with a smoker during pregnancy) and also other potential confounders or effect measure modifiers such as maternal smoking, alcohol consumption, marital status, household income, fast food consumption, prenatal vitamin use, and work status during pregnancy. We used this dataset in the analysis of indoor air quality and birth outcomes.

Air pollution exposure assessment overview

We used three distinct exposure assessment methods in these studies:

1. CARB ambient air monitoring data from 4 LA County sites that measured air toxics as well as criteria air pollutants (Azusa, Burbank, Downtown LA, North Long Beach). Because we are using monitoring station data to provide estimates of air pollution exposures, we restricted the dataset to only those subjects who resided within 5 miles of one or more of the 4 monitoring stations measuring air toxics. Similar method has been used in our previous studies using monitoring station data, with varying radii for inclusion, and is thought to reduce exposure misclassification.[3,53,60] Exposure averages were created for several pregnancy periods of interest, including each trimester, the first month, and last month of pregnancy. We used two different types of air pollution averages in the analysis: (1) scaled by the inter-quartile range calculated separately for each pollutant-pregnancy period combination, and (2) continuous measures based on previously-determined unit measures for each pollutant. The air toxics dataset allowed us to

examine the effects of key volatile organic compounds (VOCs), namely BTEX, specific PAHs known to have carcinogenic effects (benzo(a)pyrene (BAP) and benzo(g,h,i)perylene (BGP)), and a metal shown to have adverse effects on birth weight in animal models (vanadium).[61] This exposure dataset was used in the studies of air toxics and LUR-modeling approaches on term LBW and preterm birth.

2. LUR-modeled estimates of NO, NO_2, and NO_x were extracted from the LA County LUR model, which was developed as a joint effort between Drs. Beate Ritz and Michelle Wilhelm at UCLA and Drs. Michael Jerrett and Jason Su at UC Berkeley.[58] This LUR model was based on physical measurements from 2006-2007, in locations across LA County. LUR estimates of air pollution represent annual averages. Because we are interested in medium-term exposures during pregnancy, we also used a seasonalized version of the LUR model when analyzing pregnancy-period specific exposures. Briefly, the seasonalization method used data from the CARB air monitoring stations to weight the exposure estimate based on the start and end dates of the subject's pregnancy periods of interest (e.g. first trimester, last pregnancy month). This exposure modeling approach was used in the studies of air toxics and LUR-modeling approaches on term LBW and preterm birth.

3. We used data from the EPOS survey to create indoor air quality summary measures. We evaluated the effects of two sources of indoor air pollution (e.g.

environmental tobacco smoke (ETS) and VOC-containing personal and household products (e.g. nail polish, hairspray, and insect spray)), as well as the effects of home ventilation.

Statistical methods overview

Standard logistic regression methods were used in the study of air toxics and LUR-based exposure estimates on term LBW, and the study of indoor air quality on preterm birth and term LBW. Conditional logistic regression was used in the matched case-control study of air toxics and LUR-based exposure estimates on preterm and very preterm birth.

In each of the studies, individual air pollutants were first examined separately. In the air toxics analysis, where we will have pollutant averages for several different pregnancy periods, we will examine associations for each of these pregnancy periods separately. We additionally analyzed the air toxics and LUR exposures on preterm birth using two-pollutant models, excluding pairs of pollutants that covaried strongly within the pregnancy period. Confounders were selected to be included in the models based on *a priori* hypotheses and the change in the effect measure estimates when including or excluding a variable of interest.

We conducted several stratified analyses to explore differences in effect estimates across groups (e.g. race/ethnicity, time period). In the studies using air toxics monitoring data, stratifying by station additionally allowed us to evaluate purely temporal fluctuations of air pollution, independent from spatial variations. In the analysis of indoor air quality, we stratified regression models by whether or not the mother worked outside the home; this stratification is intended to show whether the air pollution effects

are stronger or more consistent for women who presumably spend more time at home, and therefore would be less susceptible to exposure misclassification.

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Chapter 2
Summary of the Literature

Ambient air pollution and adverse birth outcomes (IUGR and preterm birth)

A growing number of studies have linked prenatal ambient air pollution exposures to intrauterine growth retardation (IUGR) and preterm birth.[1-3] Epidemiologic studies have been conducted in many countries with different populations, and the evidence suggests that outdoor air pollution plays some role in determining birth outcomes. Yet, the differences in specific pollutants, outcomes, and pregnancy periods studied make synthesis difficult and causal interpretations of the observed associations remain a subject of ongoing discussions. Most previous studies have focused on criteria air pollutants (i.e., CO, PM_{10}, $PM_{2.5}$, NO_2, O_3 and SO_2) rather than specific air toxics due to a lack of measurement data or validated models to estimate source-specific exposures such as motor vehicle exhaust.

Studies conducted in the Los Angeles Air Basin showed positive associations between average CO concentrations during the third trimester of pregnancy and term LBW[4] and between CO, PM_{10} and $PM_{2.5}$ concentrations early in pregnancy and six weeks prior to birth and prematurity.[5,6] One study also reported a dose-response relationship between CO during the second month of pregnancy and cardiac ventricular septal defects.[5] CO is also a major constituent of tobacco smoke, is shown to cross the placenta, bind to haemoglobin to form carboxyhaemoglobin (COHb), and thereby reduce the amount of oxygen available to the fetus.[7,8] Environmental tobacco smoke has also been strongly linked to reductions in birth weight.[9-16] However, the CO concentrations found

in smoking or ETS exposures (~60-65ppm)[8] are several orders of magnitude greater than concentrations found in ambient air (~5ppm),[4] which is inconsistent with the observed effects on birth weight and preterm birth risk. Therefore, the current hypothesis is that CO is a traffic marker rather than the causative agent for these birth outcomes. Studies linking residential proximity to heavy traffic to adverse birth outcomes[17] also support this hypothesis that unmeasured components of vehicle exhaust correlated with CO and particle mass are causative agents. Also, the size of observed associations increased when the analyses were restricted to women living in closer proximity to a monitoring station[6] and to women who did not work outside their homes while pregnant,[18] suggesting that exposure estimates for pollutants with marked spatial variability (such as toxics in motor vehicle exhaust) more accurately reflected actual exposures for these women. This finding not only underscores that specific air toxics associated with motor vehicle emissions may adversely affect fetal health in LA, but also that spatially refined models are needed to advance this field.

Exposure assessment for motor vehicle exhaust toxins

Almost all existing studies of air pollution and birth outcomes used ambient air monitoring data to assess exposure, a method that is limited by its inability to capture fine spatial variations in primary exhaust pollutants. Measurement data indicate concentrations of certain motor vehicle exhaust constituents such as CO, NO_x and primary UF (i.e., UF emitted directly in vehicle exhaust and not formed through atmospheric reactions) and adsorbed species such as PAHs are most elevated near their roadway sources and exhibit considerable spatial variability over short distances—

variability that is not well-reflected in community-wide air monitoring data.[47-63 19-35] Since personal measurements of UF, PAHs, EC/OC and other traffic exhaust constituents are too costly and logistically difficult to obtain in large population-based epidemiologic studies, especially over time periods longer than 48 hours which would be relevant to pregnancy studies, a number of surrogate exposures measures have previously been employed. Most of these have been relatively simple (e.g., residential distance to roadways, traffic counts on roadways near homes, self-reported traffic density on street of residence) and usually have not been validated with residential or personal air pollution measurements.

A novel approach for assessing exposure to traffic exhaust pollutants – land use-based regression (LUR) modeling – has been applied in Europe,[36-41] Canada,[42,43] San Diego, California,[44] and most recently in LA County by our research group.[45,46] This approach incorporates outdoor pollution measurements taken at many locations throughout an urban area, in addition to Geographic Information System (GIS) predictors of traffic exhaust concentrations (such as traffic counts, truck routes, and roadways). The results of LUR modeling are air pollution surfaces (i.e. maps) for the geographic region, from which estimates of longer-term air pollution exposure is extracted for individuals, typically based on their GIS-mapped residential address locations (although other locations, such as school or workplace, can be used). These models have been shown to have good predictive capability. For example, in a recent model developed for San Diego, California, 79% of the variation in NO_2 levels measured at 39 locations was predicted by various GIS traffic parameters.[44] Our model in LA County based on over 200 measurement locations in two seasons and explained 81%, 86% and 85% of the variance

in measured NO, NO_2 and NO_x concentrations, respectively.[47] These modeling efforts to date have focused on NO_x, $PM_{2.5}$, benzene and black carbon measurements as markers of exhaust toxics. Only a handful of birth outcomes studies have employed LUR modeled estimates of air pollution, and the only studies conducted in the U.S. were recently completed by our research group.[45,46]

Evidence from epidemiological and animal studies

There are some limited animal and epidemiologic data on specific motor vehicle toxics and their relations with adverse birth outcomes, with the most evidence supporting a role for PAHs, and some limited evidence suggesting benzene toxicity in fetal development. Experimental and human data indicate PAHs can cross the placenta and reach fetal organs.[48-53] Animal experiments have linked PAH exposure to stillbirths, fetal absorption, congenital abnormalities and decreases in fetal weight.[54] While specific mechanisms are unknown, as summarized by Perera et al.,[55] current hypotheses include anti-estrogenic effects,[56] binding of constituents to the human aryl hydrocarbon receptor to induce P450 enyzmes that catalyze oxidation,[57] and DNA damage resulting in activation of apoptotic pathways.[58-60] Dejmek et al.[60] proposed PAHs may directly affect early trophoblast proliferation due to their reaction with growth factor receptors,[61,62] causing suboptimal placentation, reduction in exchange of oxygen and nutrients with the fetus, and impairment of fetal growth.

PAHs and metals can attach to ultrafine (UF) particles (<0.1 μm in diameter), be inhaled into the body, and trigger an oxidative stress response. Measurement studies undertaken by UCLA investigators at urban sites in LA indicate a large portion of UF

consist of organic carbon (OC), followed by EC as primary products from vehicle emissions and that UF contain the largest fraction of PAHs by mass.[63-65] Organic components of PM, which comprise a large proportion of freshly emitted exhaust and secondary aerosols, have been shown to induce a broad polyclonal expression of cytokines and chemokines in respiratory epithelium.[63,66,67] This may be due to the action of PAHs, metals and related compounds that lead to the production of cytotoxic reactive oxygen species (ROS). Such inflammatory and oxidant stress responses are expected to occur at extrapulmonary sites as well. For example, it has been hypothesized that preterm birth can be triggered by abnormal cytokine production favoring inflammation, yet inflammatory cytokines may be a normal component of the body's preparation for parturition.[68,69] An alternative hypothesis is that air pollution may increase anti-inflammatory cytokines in the lower genital tract, thereby increasing the risk for infection, which could lead to preterm birth.[70] Some preterm births may be caused by an early activation of these components generally associated with delivery.[71]

A number of epidemiologic studies support a role for PAHs in impairment of fetal growth. Dejmek et al.[60] reported an exposure-response relation between first month PM_{10}, $PM_{2.5}$, and carcinogenic PAH exposures and risk of small-for-gestational age (SGA) for births in Teplice, Czech Republic. Vassilev et al.[72,73] evaluated annual average polycyclic organic matter (POM) concentrations (of which PAHs are a major constituent) for residents of New Jersey and reported exposure-response relations with very low birth weight (<1,500g), term LBW, SGA, and preterm birth. POM concentrations were based on emissions and dispersion-model estimates but ambient measurement data were not available for validation; however, similarly modeled estimates for the air toxics benzene,

toluene, and xylenes were within a factor of two of measured concentrations. Our recent LA County studies used air toxics data from the Multiple Air Toxics Exposure Study (MATES III) and reported increased odds of term LBW with exposure to BAP and BGP ((~2-3% per interquartile range (IQR)), elemental carbon (~ 4-5% per IQR), and $PM_{2.5}$ from diesel and gasoline exhaust and paved road dust (~4-5% per IQR).[45] In the MATES-based study of preterm birth,[46] we reported 50% increased odds per IQR for BGP, 19% increased odds per IQR for BAP, and 52% increased odds per IQR for total PAHs (including BAP, BGP, and naphthalene). Increased odds of preterm birth were also associated with increased exposures to organic carbon, elemental carbon, and $PM_{2.5}$ from diesel exhaust, ammonium nitrate, biomass burning, and sea salt, although these first 3 pollutants loaded onto the same factor in a factor analysis, indicating high correlations.

The only U.S. study to collect personal measures of PAHs during pregnancy examined fine particles and PAHs in a small prospective birth cohort of approximately 500 African-American and Dominican families in New York City;[55] a similar sister study was conducted in Krakow, Poland.[74] These studies conducted personal $PM_{2.5}$ and PAH air sampling over a 48-hour period during pregnancy, and measured PAH biomarkers (benzo(a)pyrene (B(a)P)-DNA adducts) in maternal and cord blood at delivery. High prenatal exposures to eight carcinogenic PAHs during the third trimester were found to be associated with reductions in birth weight (9%) and head circumference (2%) among NYC African-Americans.[75] Also, combined exposure to both high ETS and B(a)P-DNA adducts had a significant multiplicative effect on birth weight (7% reduction) and head circumference (3% reduction) in both African-Americans and Dominicans.[55] Prenatal

PAH exposure was 10-fold higher in Krakow, Poland than in NYC[76] and found to be associated with significantly reduced birth weight.

Very few studies have examined relations between specific air toxics other than PAHs and adverse birth outcomes. Most epidemiologic studies of organic solvents have been conducted in occupational settings, and have reported increased risks of spontaneous abortion, small for gestational age (SGA), preterm birth, and birth defects, and reductions in birth weight.[77-88] A Finnish population-based study of work exposure to organic solvents found increased odds of SGA with exposures 3 months before or during pregnancy (OR=1.67, 95% CI=1.02, 2.73), and a small statistically non-significant increased odds of LBW (OR=1.17, 95%CI=0.71, 1.93).[77] Two studies found that exposures to occupational-use solvents increased the risk of spontaneous abortions,[85,86] and one study additional assessed non-occupational use of solvents, reporting mostly null associations, although women who used solvents in both occupational and non-occupational settings had greater odds of spontaneous abortion compared to women who used solvents exclusively at work.[85] Chinese women in a petrochemical facility exposed to benzene had a 0.29 week (SE=0.12) decrease in length of gestation compared to unexposed women.[87] In particular, the study reported that highly exposed women with susceptible CYP1A1 and GSTM1 genotypes, which affect an individual's ability to detoxify benzene, had larger decreases in gestational age. These investigators noted that although the leftward shift in gestational age seems relatively small, it might be important for pregnancies already at high risk for prematurity. Several others focused on occupational exposures among either parent and risk of birth defects.[78-81]

There are a small number of non-occupational studies that have examined benzene exposure and adverse birth outcomes. A small French study of 271 nonsmoking women, and assessing benzene exposure using personal monitoring, reported that exposures in the 2nd and 3rd trimesters of pregnancy were associated with decreases in head circumference at birth, second and third trimester ultrasounds, biparietal diameter in ultrasounds in each trimester, and birth weight, although confidence intervals crossed the null for some associations.[89] Most recently, a smaller Spanish study using LUR models of both NO_2 and benzene reported increased risk of preterm birth among women highly exposed to NO_2 in the second and third trimesters, and those highly exposed to benzene averaged over the entire pregnancy, although benzene exposures were strongly correlated across pregnancy periods (r~0.72-0.91), limiting their ability to identify confidently periods of greater sensitivity to pollution exposure.[41] Our recent MATES-based study in LA County found positive associations with benzene and preterm birth (~9% increased odds per IQR), but not with term LBW.[45,46] In experimental studies, benzene has been shown to cross the human placenta[90] and is associated with reduced fetal weight in animal models.[91] While the biological mechanisms are unknown, benzene can form DNA adducts which can alter enzyme formation and lead to cell death,[91] and metabolites of benzene can cause oxidative stress, which negatively impacts fetal blood cell development.[92-95]

Birth outcomes studies using land use-based regression (LUR) modeled estimates of air pollution

A small number of studies have used LUR-modeled estimates of air pollution exposure to examine associations with birth outcomes, with the majority of studies being conducted in Europe,[38-41,96,97] and only 3 studies in North America (including 2 of our LA County studies)[45,46,98]. Prior to our LA County studies, the only other North American study was conducted in Vancouver, Canada, and compared three distinct exposure assessment methods: (1) seasonalized LUR estimates of NO_2, NO, $PM_{2.5}$ and black carbon, (2) a nearest monitor approach (zipcode within 10km), and (3) an inverse distance weighted (IDW) approach using the 3 closest stations within 50km of the residential zipcode.[98] LUR-estimated entire pregnancy average $PM_{2.5}$ was associated with SGA (per 1$\mu g/m^3$, adjusted OR=1.02, 95% CI=1.00, 1.03) and term LBW risk (per 1$\mu g/m^3$, adjusted OR=1.03, 95%CI = 0.99, 1.07); NO was also associated with SGA (per 10$\mu g/m^3$, adjusted OR=1.02, 95% CI = 1.00, 1.04). Comparing results from LUR versus IDW estimates, Brauer et al. reported similar results for NO, but IDW-estimated NO_2 showed ~10% increased risk per 10 $\mu g/m^3$ compared to null associations for LUR-estimated NO_2 for both SGA and term LBW. Using the distance to roadway measure, the study showed increased risk of SGA and term LBW among women living <50m from a highway, but no association was apparent when evaluating a 150m distance from the highways; exposure assessment using distance to major road, or distance to highway or major road provided mostly null results. The authors also reported increased risk of very preterm birth (defined as <30 weeks) with LUR and IDW-estimated entire pregnancy exposures of NO, NO_2, $PM_{2.5}$, with stronger associations observed for the IDW-based measures. No particular critical window of exposure was apparent similar to our results for very preterm birth, but exposures across the pregnancy periods were highly correlated, i.e. the

influence of seasonality was minimal. The only pollutant found to be associated with preterm birth (<37 weeks completed gestation) was IDW-estimated $PM_{2.5}$.

Our recent LA County studies using LUR-estimated NO, NO_2 and NO_x reported associations with both preterm birth and term LBW.[45,46] These studies were based on a population of births defined around the availability of air toxics monitoring data from the MATES III study. The study included births spanning 22 months in 2004-2006 to correspond to the dates of available MATES monitoring data, and used monitoring station data to seasonally-adjust the LUR data. We estimated approximately 5% increased odds of term LBW per IQR increase in LUR-estimated NO, NO_2 and NO_x, for both seasonalized and unseasonalized estimates. In the study of preterm birth, LUR-estimated NO, NO_2 and NO_x were associated with 4% increased odds per IQR increase in pollutant concentration; seasonalized LUR measures had similar associations but only in multipollutant models. While some of the trimester-specific LUR exposure estimates were associated with the outcomes, the strong correlations across pregnancy periods limited our ability to make conclusions about periods of greater sensitivity to air pollution. Both these studies support the hypothesis that traffic-related air pollution has important impacts on birth outcomes.

All other LUR-based birth outcomes studies were conducted in Europe with short study periods. Overall, three studies examined measures of growth restriction, [38-40], one study examined preterm birth, [41] and two studies examined both types of outcomes.[96,97] All these studies reported strong correlations across trimester-specific and entire pregnancy average exposure estimates, thus hindering their ability to identify conclusively any specific periods of greater sensitivity. Two Spanish studies used

seasonalized LUR models based on NO_2[38,39] and BTEX[38] measurements to examine associations with growth restriction. One study based in Sabadell, Spain reported reductions in birth weight associated with entire pregnancy average BTEX and NO_2, but only for women who spent <2 hours in nonresidential outdoor locations.[38] The other study based in Valencia, Spain found first trimester and entire pregnancy NO_2 to be associated with decreases in birth weight, and birth length, and SGA.[39] Another study using the same cohort based in Valencia, Spain used LUR models of NO_2 and benzene reported increased risk of preterm birth among women highly exposed to NO_2 in the second and third trimesters, and those highly exposed to benzene averaged over the entire pregnancy.[41] A German cohort study used seasonalized LUR models based on NO_2 and $PM_{2.5}$ measurements, and reported increased risk of term LBW with entire pregnancy average NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance.[40] Two Dutch studies based on large cohorts used seasonalized LUR models, with one study reporting no increased risk of preterm birth, SGA, or term birth weight reductions with LUR-estimated NO_2.[97] The other Dutch study reported detrimental effects on term birth weight and preterm birth with LUR-estimated NO_2, $PM_{2.5}$, and soot exposures last pregnancy month and entire pregnancy, with 95% CI's spanning the null; first trimester LUR-estimated exposures were also associated with term birth weight reductions, again, with 95% CI's spanning the null.[96]

Indoor air quality and adverse birth outcomes (IUGR and preterm birth)

Combustion products, including tobacco smoke, emit a mixture of gases and fine particles in the air. Of particular interest to birth outcomes researchers are fine particles ($PM_{2.5}$), CO, PAHs (e.g. benzo(a)pyrene), and VOCs, including benzene and styrene[99].

Smoking in confined spaces results in very high $PM_{2.5}$ concentrations, but ventilation has been demonstrated to reduce $PM_{2.5}$ levels.[100] It is well understood that maternal smoking is linked to increased risk of preterm birth and intrauterine growth restriction (IUGR), as well as other adverse birth outcomes.[101] Studies of environmental tobacco smoke (ETS) suggest a consistent increased risk for low birthweight.[11,12,14] In contrast, studies of ETS and preterm birth are somewhat less consistent.[15,101] One study reported an almost two-fold increased risk of preterm birth with ETS exposure for mothers aged 30 years and older, but no effect for younger mothers.[13] A large California study using cotinine as a marker of ETS exposure reported large increases not only in preterm birth risk, but also fetal death and term LBW, and observed a linear dose-dependent relationship with mean birth weight and mean infant length.[10]

VOCs found in some personal and household products (e.g. nail polish or remover, hairspray, cleaners, insect spray) may include acetone, 2-butanone, benzene, toluene, xylenes, formaldehyde, and other chemicals.[102-105] As discussed in the previous section, benzene has been linked to reported increased risks of spontaneous abortion, small for gestational age (SGA), preterm birth, and birth defects, and reductions in birth weight, mostly in occupational studies or studies of ambient air pollution.[38,46,77-89] An older study of spontaneous abortion reported mostly null associations with non-occupational use of solvents, although women who used solvents at work and at home had larger increases in odds of spontaneous abortion compared to women who used solvents only at work.[85] A recent study based on the Danish National Birth Cohort (DNBC) examined exposure to paint fumes due to renovation activity at home, and reported a lower risk of SGA, and no association with preterm birth or birth weight.[106]

These two studies are the only studies we are aware of that are a population-based epidemiologic study of non-occupational indoor air quality impacts on birth outcomes, beyond studies focusing on ETS.

Residential-use insect sprays once commonly contained organophosphates, although these are being replaced by pyrethroids.[107] Studies have linked prenatal exposure to certain organophosphates to impaired fetal growth and mental development in children.[108-110] Studies have reported a significant multiplicative interaction between ETS and BAP-DNA adducts on fetal growth, suggesting that PAHs from tobacco smoke, pesticides and/or air pollution from outdoor sources are all important to consider.[55,111] Other studies of pesticide exposures suggest a possible interaction between paraoxonase (PON1) polymorphisms and pesticide exposure resulting in restricted fetal growth.[112,113]

And finally, outdoor sources of air pollution may affect indoor air quality. In the Los Angeles Basin, one study found that indoor sources of "quasi-ultrafine" particles (<0.25 μm diameter) were not significant contributors to personal exposure, and that both outdoor and indoor concentrations of CO, NO_2, and NO_x were more positively correlated to "quasi-ultrafine" particles than $PM_{2.5}$ or PM_{10}.[114] The Relationship of Indoor, Outdoor and Personal Air (RIOPA) study conducted 48-hour sampling at 310 non-smoking households in Houston, Texas, Los Angeles, California, and Elizabeth, New Jersey, to compare indoor, outdoor, and personal exposures to air pollutants.[115] The RIOPA study reported that the measure of personal exposure to $PM_{2.5}$ was higher than outdoor measurements, which were slightly higher than indoor measurements.[116] While outdoor air pollution was the largest contributor to both indoor and personal $PM_{2.5}$ exposures, some indoor personal activities were important contributors (e.g. woodworking,

smoking).[117] Another study of indoor, outdoor, and personal exposures to VOCs in Minnesota non-smoking adults (n=71) reported personal exposures to be higher than indoor or outdoor concentrations of VOCs, although indoor concentrations provided a better estimate of personal exposures compared to outdoor measurements.[118] Two Spanish studies conducted short-term passive sampling of indoor and outdoor NO_2 and found that outdoor levels of NO_2 were greater than indoor levels.[119,120] However, one of these studies reported that those who lived in a rural area had higher indoor than outdoor NO_2, and also found no correlation between home ventilation or parental smoking habits with indoor NO_2 concentrations.[120] These data suggest that outdoor vehicle exhaust may be an important contributor to indoor air quality.

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Chapter 3

Comparing GIS-based and air toxics exposure measures of traffic-related pollution: a study of term low birth weight in Los Angeles County, California

ABSTRACT

Few birth outcomes studies have examined associations with air toxics in traffic exhaust. Additionally, land use-based regression (LUR) provides estimates of small area variation in air pollution and contributes to an understanding of the spatial distribution of traffic-related air pollution. The authors included 8,181 term low birth weight (LBW) cases and 370,922 term normal-weight non-cases born between 1/1/1995-12/31/2006 to women residing within 5 miles (8km) of an air toxics monitoring station in Los Angeles County, California. LUR-modeled estimates of NO, NO_2 and NO_x were seasonalized using monitoring station data, and extracted for geocoded residential addresses. Associations with term low birth weight (LBW, ≥37 weeks completed gestation and <2500g birth weight) were examined using logistic regression adjusted for maternal age, race/ethnicity, education, parity, and infant gestational age and gestational age squared. For seasonalized LUR-estimated and air toxics exposures, the strongest associations were seen for the third trimester, the entire pregnancy, and the last pregnancy month averages. A 10ppb increase in unseasonalized LUR estimates was associated with 4-12% increased odds, in adjusted models. Third trimester benzene, toluene, ethyl benzene, and xylene exposures were associated with term LBW when stratified by closest monitoring station. Using spatial contrasts (e.g. unseasonalized LUR estimates) and temporal contrasts (e.g.

monitoring station estimates, stratified by station), the study provides additional evidence that traffic-related air pollution increases the risk of term LBW.

INTRODUCTION

For more than a decade, epidemiologic studies have linked prenatal air pollution exposure to a variety of adverse birth outcomes, including low birth weight, small for gestational age (SGA), preterm birth, and cardiac birth defects[1-4]. Links between prenatal exposure to carbon monoxide (CO), particles (PM_{10}, $PM_{2.5}$), and polycyclic aromatic hydrocarbons (PAHs) and intrauterine growth restriction point to toxins in motor vehicle exhaust as possible causative agents.[2,5,6]

Most studies relied on data from government air pollution monitoring stations which typically measure only "criteria" air pollutants (CO, NO, NO_2, NO_x, ozone and PM) used for regulatory purposes, and exposures estimates are often assigned based on residential zip codes at birth.[7,8] However, this method of exposure assessment has two major limitations: (1) it results in limited spatial resolution for primary traffic pollutants;[9,10] and (2) air toxics, such as PAHs,[11,12] which are correlated with, and coming from, the same sources as some of the criteria pollutants may, in fact, be the causative agents for these birth outcomes. Few population-based studies of birth outcomes have examined air toxics exposures, most likely because data on these pollutants are collected at few government monitoring stations.

To achieve better spatial resolution for primary traffic pollutants, a few studies recently have employed land use-based regression (LUR) methods to model traffic related prenatal air pollution exposures on a finer spatial scale, and adjusted the LUR model estimates to account for seasonal fluctuations.[13-18] However, only one study compared results from LUR-estimated exposures to any other exposure assessment

method in examining the importance of both spatial and temporal variations in air pollution in the same study population.[18]

In this paper, we use three sources of air pollution exposure data in the Los Angeles air basin: 1) ambient criteria pollutant data; 2) air toxics monitoring data; and 3) a LUR model measure for traffic-related air pollution "seasonalized" to represent temporal variations, to estimate and compare the effects of air pollution on birth weight in full term births.

MATERIALS AND METHODS

Birth certificate data and outcome assessment

We used electronic birth certificate data from the State of California to identify women who gave birth between 1/1/1995 to 12/31/2006 while residing in Los Angeles County, California (n= 1,745,754). From these birth certificates, we obtained the mother's address at the time of birth, as well as information about maternal age, race/ethnicity, education, parity, prenatal care initiation and payment source, number of gestations, baby's gestational age at birth, birth weight, sex, birth defects, and date of birth. We used gestational age information to identify preterm babies (<259 completed gestational days) and low weight babies (<2500g). We excluded births with recorded defects (n=85,114), missing gestational ages (n=81,072), extreme gestational ages (<140 days, or >320 days) (n=19,139) or birth weights (<500 g, or >5,000 g) (n=3,125) likely due to recording or reporting errors, and multiple gestations (n=32,425).

All addresses were geocoded using the University of Southern California GIS Research Laboratory geocoding engine.[19] Geocoding quality flags are shown in

Supplement Table 3-6. We excluded 2,612 non-geocodeable addresses, and conducted sensitivity analysis excluding the <7% poorer quality geocoded addresses, but this exclusion did not change our results. Address locations were mapped in ESRI ArcGIS software, and overlaid with the geocoded CARB air toxics station locations in LA County. From among all women with geocoded addresses (n=1,522,627), we included in our analyses only those who resided ≤5 miles (8km) of a CARB air toxics monitoring station (n=415,531, 27.3%). This radius was selected to balance sample size needs versus the potential for exposure misclassification.

In this paper, we compared term LBW cases (infants born at term but weighing less than 2500g, n=8,181) to infants born at term and at or above 2500g (n=370,992 non-cases), excluding all preterm births (n=36,428). A sub-cohort of year 2000-2006 births (used for LUR analyses) included n=4,895 term LBW cases, and 217,717 non-cases.

Exposure assessment

The California Air Resources Board (CARB) maintains four air toxics monitoring stations in Los Angeles County. Three stations were active over the entire study period (Downtown LA, Burbank, and north Long Beach), while one station provided measurements from 2000-2006 only (Azusa) (Figure 4-1). Measurements for benzene, toluene, ethyl benzene, and xylene (BTEX) were available for the entire study period, but PAH measurements ceased in December 2004, and vanadium measurements in late February 2003. $PM_{2.5}$ measurements began in January 1999, and there are several months of missing data within our study period for the Burbank station (missing

1/1/2000-3/19/2000 and 5/18/2000-7/11/2000). These stations also collected criteria pollutant data.

Exposure estimates were averaged the 1st, 2nd and 3rd trimester, entire pregnancy, and the last 30 days before birth ("last pregnancy month") for each pollutant examined. For criteria pollutants, pregnancy period averages were created for CO, NO, NO_2, NO_x, ozone, PM_{10}, and $PM_{2.5}$. For the gaseous pollutants (hourly data), 24-hour averages were first created and further averaged over the pregnancy periods. For air toxics, averages were created for two PAHs previously suggested to have important health effects (benzo(a)pyrene (BAP) and benzo(g,h,i)perylene (BGP)), total PAHs (BAP, BGP, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenz(a,h)anthracene, and indeno(1,2,3-cd) pyrene), benzene, ethyl benzene, m,p-xylene, o-xylene, toluene, and vanadium. We applied exclusion criteria per pollutant based on having >50% of the available measurements over the pregnancy period (Supplement Table 3-7).

Most subjects lived within 5 miles (8km) of only one air toxics station, but 3,506 women (0.9%) lived within 5 miles (8km) of both the Burbank and Downtown LA stations. For these women, we created daily averages when air pollution data was available from one or both stations, weighted by the inverse of the distance to the station.

LUR model and seasonalization

We estimated traffic air pollution exposures using LUR models previously developed for the LA Basin.[20] Because the LUR models were based on measurement data collected in 2006-2007, we restricted the LUR analyses to births in the years closest to this time period (2000-2006). The LUR model was developed based on >200 monitoring

locations throughout LA County, and explained 81%, 86% and 85% of the variance in measured NO, NO_2 and NO_x concentrations, respectively.[20]

We overlaid the geocoded residential addresses from the birth certificate with the LUR surfaces to assign estimated exposures. The LUR models were developed to assess long-term exposures and most closely approximate annual average concentrations. Therefore, in addition to the LUR annual average estimates ("unseasonalized estimates"), we created "seasonalized" LUR measures using measurement data from the air monitoring station(s) within 5 miles (8km) of the woman's home address. Specifically, the LUR estimates were adjusted (multiplied) to generate pregnancy-month specific LUR values as follows: first month seasonalized NO_x average = LUR NO_x * (first month air monitoring station average NO_x/2006-2007 air monitoring station annual average NO_x). The "seasonalized" pregnancy month LUR values were then averaged over the pregnancy periods of interest.

We applied the same hourly and daily exclusion criteria as described above when generating the pregnancy month scaling factors for NO, NO_2 and NO_x. The scaling factors for women within 5 miles (8km) of two stations were based on a weighted average of values from both stations, again using the same method as above for criteria pollutant exposures.

Statistical Analysis

All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). We plotted pollutant measures to examine trends over time and across the four

monitoring stations. Pearson's correlation coefficients were used to assess collinearity across pollutant estimates and pregnancy periods.

Standard logistic regression methods were used to estimate increases in risk of term LBW per unit or interquartile range (IQR) increase in pregnancy-period toxin exposures. We adjusted for several potential confounders that were important in our previous studies of air pollution and birth outcomes[21]— maternal age, race, education, parity, and gestational age (see Supplement Figure 3-2) – and examined changes in air pollution effect estimates with adjustment for other variables, including mother's birthplace and a previously-developed metric of socioeconomic status (SES) based on Census block group data, where the block groups were categorized into quintiles based on the SES score.[22,23] Because the birthplace and SES variables did not change the air pollution effect estimates by more than 5%, the variables were not included in the final models. See Supplement Figure S-1 for a diagram of the relationships among key variables in the study.

RESULTS

Seasonal trends and correlations across air pollutants

All air toxics except vanadium showed strong seasonal trends, with peak levels occurring in the winter. Benzene levels decreased by about 65% and PAHs also decreased about 40% over the 12 year study period. On average, the highest levels of BTEX were measured at the Burbank and Downtown LA stations, while PAHs were highest in Burbank. Vanadium levels were highest on average in North Long Beach.

Seasonalized LUR-based exposure estimates were moderately correlated with all measured air toxics (r~0.34-0.60) except vanadium, most likely because these pollutants were selected because they are important components of traffic exhaust – a major contributor to air pollution in the LA basin.[24] While vanadium is found in traffic exhaust, industrial sources and shipping emissions may be more significant contributors.[25] Unseasonalized LUR exposure estimates correlated only with seasonalized LUR estimates (r = 0.45-0.75), and not with any of the measured air toxics (Table 3-1). Toxics were strongly correlated within each pollutant class (PAHs, BTEX), but vanadium showed moderate negative correlations with PAHs, benzene, and ethyl benzene (r ranging from -0.29 to -0.57), and positive correlations with m,p-xylene (r = 0.55).

Pollutant estimates were correlated across pregnancy periods (Table 3-2), with moderate to strong positive correlations between 2nd trimester and entire pregnancy averages, and between 3rd trimester and last month of pregnancy averages, for both measured and LUR-estimated pollutants (Table 3-2). First trimester averages were negatively correlated with 3rd trimester average NO, BAP, and benzene, but positively correlated with entire pregnancy averages. Entire pregnancy NO_2 was positively correlated with NO_2 in each trimester (r = 0.69-0.88), for both measured and LUR-estimated averages.

Term LBW Results

Of the nearly 400,000 births from 1995-2006, the largest number of births occurred in the Downtown LA area (3,505 cases, 150,384 non-cases), followed by North Long Beach (1,827 cases, 79,920 non-cases). Approximately 70% were Hispanic, and

over 60% of mothers were born outside of the U.S. (Table 3-3) The majority of mothers initiated prenatal care in the first trimester (86.6%), and 61.8% were multiparous. Prenatal care was covered by private insurance for 37.1%, while government (including Medicaid) or non-government programs covered 60.1% of the mothers. Approximately half the mothers (51.1%) completed high school or beyond, and just over half (52.8%) were between the ages of 20 and 29 years at delivery. The overall prevalence of term LBW in our study was 2.2%. Univariate models indicated higher odds of term LBW for infants born to mothers under age 20 years, nulliparous mothers, mothers receiving late or no prenatal care, US-born mothers, and mothers who used public insurance or had no insurance coverage for prenatal care. Non-Hispanic white mothers had the lowest risk of term LBW, and African American mothers had more than double the odds of term LBW, compared to non-Hispanic whites. While Hispanic mothers were 25% more likely to deliver a term LBW baby compared to non-Hispanic whites, Mexican-born Hispanics had a lower risk compared to US-born Hispanics (results not shown).

Seasonalized LUR exposure estimates were associated with increased odds of term LBW for the entire pregnancy, each trimester and in the last month of pregnancy. The strongest associations were seen for the entire pregnancy, third trimester, and last month averages. Table 3-4 shows the adjusted odds ratios (aOR) and 95% confidence intervals (CI) using continuous scaling units. For third trimester averages, we observed 1-5% increased odds of term LBW per 10 ppb increase in seasonalized LUR-estimated pollutant concentrations, and approximately 5% increased odds per IQR increase. Results for NO, NO_2, and NO_x based on monitoring station data were similar to seasonalized LUR results (Table 3-4). In addition, unseasonalized LUR exposure

estimates were associated with approximately 6-7% increased odds per interquartile range increase in pollutant concentration (Table 3-5).

Several measured air toxics also showed associations with term LBW risk, particularly benzene, m,p-xylene, o-xylene, and toluene exposure estimates in late pregnancy (Table 3-5). Additionally, interquartile range increases in each of the PAH measures and ethyl benzene in the last month of pregnancy (Supplement Table 3-8) were associated with small increased odds of term LBW (aOR (95% CI): BAP aOR=1.02 (1.00, 1.04), BGP aOR=1.02 (1.00, 1.04), total PAH aOR=1.02 (1.00, 1.04), ethyl benzene aOR=1.03 (1.01, 1.06)). All measured air toxics showed null associations for the first and second trimester exposure averages, and across the entire pregnancy (results not shown). Consistent with previous studies using criteria pollutant data,[7,26,27] ambient CO, NO, NO_2, NO_x, PM_{10} and $PM_{2.5}$ were also associated with increased odds of term LBW for the third trimester, last month of pregnancy, and entire pregnancy averages.

In adjusted models stratified by closest air monitoring station, odds of term LBW were positively associated with unseasonalized LUR NO, NO_x, and NO_2 exposure estimates for North Long Beach and Downtown LA stations (Table 3-5). For the seasonalized LUR estimates, women assigned to the Downtown LA station had approximately 5-10% increased odds of term LBW per IQR increase for entire pregnancy, third trimester, and last month averages. PAH exposure estimates were generally higher for women living near the Burbank station compared to other stations, and we observed moderate increased odds in the third trimester for BAP (aOR=1.03, 95% CI= 0.95, 1.11)), BGP (aOR=1.07, 95% CI= 0.99, 1.15)) and total PAHs (aOR=1.05, 95% CI=0.97, 1.14). Increased exposure to vanadium was positively associated with

term LBW odds for women residing within 5 miles (8km) of the North Long Beach station in the first (aOR=1.04, 95% CI =0.99, 1.10) and second (aOR=1.06, 95% CI=1.00, 1.12) trimesters, as well as with entire pregnancy averages (aOR=1.08, 95% CI=1.00, 1.17).

Analyses stratifying by decade of birth (1995-1999 vs 2000-2006) showed few differences across strata except perhaps slightly stronger associations for BTEX pollutant exposure in the last month of pregnancy for 1995-1999 compared to 2000-2006, though confidence intervals overlapped (results not shown).

DISCUSSION

Our results provide new evidence for a contribution of traffic exhaust to term LBW, including long-term local exposures (represented by the unseasonalized LUR estimates), shorter-term local exposures (represented by the seasonalized LUR estimates), and shorter-term regional exposures (represented by ambient air toxics and criteria pollutant measurements). Mothers residing in LA near air toxics monitoring stations who delivered at term had greater odds of delivering a low weight baby when exposed to higher levels of traffic exhaust pollutants in the third trimester or last month of pregnancy. We observed approximately 5% increased odds of term LBW per interquartile increase in both seasonalized and unseasonalized LUR-modeled levels of NO, NO_2, and NO_x, and 2-5% increased odds per interquartile increase in measured PAHs, benzene, m,p-xylene, o-xylene, and toluene.

The consistent associations with the LUR-based exposure estimates highlight the importance of spatial contrasts in air pollution in Los Angeles, while the air toxics results

stratified by monitoring station underscore the contributions of seasonal influences within each local area. That is, stratifying the analysis by air monitoring station effectively restricts the comparisons to seasonal contrasts only, while our unseasonalized LUR exposure estimates rely solely on fine spatial contrasts in each station-specific geographical area. Because we observed positive associations using both temporal and spatial contrasts despite low correlations across measures, these results suggest that both spatial and temporal variability are important. Differences in effect measures across our four air toxics monitoring areas may result from lack of spatial or temporal variation for certain exposures within an area, or demographic differences in the population of women. The associations observed for LUR-based estimates for the Downtown LA station were stronger and had narrower confidence intervals than for the other stations – most likely a result of having the largest number of births near this station, as well as vehicle traffic being the overwhelming source of air pollution in this area. Additionally, because seasonal peaks of vanadium in the North Long Beach area provide the best exposure contrasts for this pollutant in our dataset, it is not surprising that we observed associations for vanadium primarily for births close to this station, which is approximately 7 miles (11.3km) north of the Ports of Long Beach and Los Angeles, where vanadium is emitted from burning residual oil by ships.[24,28] While we also observed large exposure contrasts for vanadium at the Azusa station, effect estimates for women residing near this station were unstable due to the limited years of data available and the small sample size. PAHs exhibit very strong seasonal variations due to seasonal inversion patterns and photochemical reactions in the atmosphere.[29,30] In our dataset, we observed the greatest

exposure contrasts and effect estimates at the Burbank station, perhaps due to its location in the San Fernando Valley, and local industrial sources.

Previous studies of criteria air pollution and term LBW or growth restriction reported increased risks with higher traffic-related exposures in the third trimester of pregnancy and/or entire pregnancy average exposures, similar to our results, and suggest that these pollutants could be acting as markers of traffic exhaust.[7,26,27] Very few birth outcomes studies used LUR techniques to model pregnancy exposure to traffic pollution, and most of these studies were not able to identify critical windows of exposure for these outcomes. The only other North American study was conducted in Vancouver, Canada, and compared seasonalized LUR estimates of NO_2, NO, and $PM_{2.5}$, a nearest monitor approach (zipcode within 10km), and an inverse distance weighted (IDW) approach using the 3 closest stations within 50km of the residential zipcode.[18] LUR-estimated entire pregnancy average $PM_{2.5}$ was associated with SGA and term LBW risk; NO was also associated with SGA. Comparing results from LUR versus IDW estimates, Brauer et al. reported similar results for NO, but IDW-estimated NO_2 showed ~10% increased risk per 10 $\mu g/m^3$ compared to null associations for LUR-estimated NO_2 for both SGA and term LBW. In contrast, our LUR-estimated results are quite similar to monitoring station results (Table 3-4). This difference may be due to better exposure contrasts in our LA County dataset, and a more refined location definition for the monitoring station data based on geocoded addresses and a maximum 5 mile radius from the monitoring station.

All other LUR-based birth outcomes studies were conducted in Europe with short study periods. Two Spanish studies used seasonalized LUR models based on NO_2[16,17] and BTEX[17] measurements. One study reported reductions in birth weight associated

with entire pregnancy average BTEX and second trimester and entire pregnancy NO_2, but only for women who spent <2 hours in nonresidential outdoor locations.[17] The other study found first trimester and entire pregnancy NO_2 to be associated with decreases in birth weight, and birth length, and SGA, but exposure estimates were strongly correlated across pregnancy periods.[16] A German cohort study used seasonalized LUR models based on NO_2 and $PM_{2.5}$ measurements, and reported increased risk of term LBW with entire pregnancy average NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance.[13] Two Dutch studies based on large cohorts used seasonalized LUR models, with one study reporting no increased risk of preterm birth, SGA, or term birth weight reductions with LUR-estimated NO_2,[14] while the other reported detrimental effects on term birth weight with LUR-estimated NO_2, $PM_{2.5}$, and soot exposures in the first trimester, last pregnancy month, and entire pregnancy, with 95% CI's spanning the null.[15]

While specific causative agents have not yet been identified, there are some animal and epidemiologic data pointing at motor vehicle toxins for adverse birth outcomes, with the strongest evidence indicating a role for PAHs.[31] PAHs have been shown to cross into the human placenta and disrupt placental perfusion, leading to intrauterine growth restriction (IUGR).[32-40] As summarized by Perera et al.,[41] current hypotheses on PAH mechanisms include anti-estrogenic effects,[42] binding of constituents to the human aryl hydrocarbon receptor to induce P450 enyzmes,[43] and DNA damage resulting in activation of apoptotic pathways.[40,44,45]

Several epidemiologic studies support a role for PAHs in impairment of fetal growth, including increased risk of SGA births[40] and term LBW.[46,47] The only US studies are based on a small prospective birth cohort in New York City,[12,41,48] which

reported third trimester exposures to PAHs (including BAP and BGP) to be associated with reduced birth weight and head circumference, and higher risks of preterm birth and SGA among African-Americans, but not Dominicans.[11,12] While we observed small increased risks of term LBW with BAP, BGP, and total PAHs, our "total PAH" measure did not include naphthalene, the most abundant PAH in the LA basin,[49] because CARB air toxics stations did not measure it. This distinction should be noted when comparing our results to other LA-based studies reporting associations between total PAHs including naphthalene and term LBW.

Very few birth outcomes studies have examined specific air toxics aside from PAHs. A small study of 271 nonsmoking women, and assessing benzene exposure using personal monitoring, reported that exposures in the 2nd and 3rd trimesters of pregnancy were associated with decreases in head circumference and birth weight, though confidence intervals crossed the null for the birth weight associations.[50] A Spanish population-based study using a LUR model[51] and a Chinese occupational study[52] reported negative effects of benzene on gestational age. In animal and experimental studies, benzene has been shown to cross the placenta[53-55] and is associated with reduced fetal weight.[56] While the biological mechanisms are unknown, it is clear that benzene can form DNA adducts, which could alter enzyme formation and lead to cell death,[56] and metabolites of benzene can cause oxidative stress, which negatively impacts fetal blood cell development.[57-60] Animal studies indicate that vanadium crosses the placenta and accumulates in fetal tissues, and a small number of studies have reported fetal loss and birth defects, though these studies only examined intraperitoneal and intravenous exposure routes, rather than inhalation.[61]

While the exposure modeling methods employed in this study improve upon most other birth outcomes studies, we acknowledge the possibility of some exposure misclassification. Exposure estimates are assigned based on the residential address listed on the birth certificate. While approximately 20% LA County women move homes during pregnancy,[21] they typically stay within the same neighborhood, so exposure estimates based on birth certificate addresses are usually similar to estimates based on actual pregnancy residences.[62,63] To account for neighborhood-level similarities in air pollution exposures and other factors, we used a mixed model clustering on zipcode and found very little difference in exposure estimates. Additionally, exposure estimates are potentially less valid for women who lived further from the monitoring station, compared to those living near the station. In sensitivity analyses restricting to women living within 3 miles (4.8km) of each of the stations, we found somewhat stronger associations with large overlap in confidence intervals, suggesting only a small degree of exposure misclassification due to residential distance from station. A third source of misclassification is due to air toxics monitoring data being available only every 12 days, and we may have missed some important peaks in toxins due to unusual events.

There are also limitations relating to using data from ambient monitoring stations and birth certificates. While these stations cover areas that are diverse in terms of race/ethnicity and SES, our results may not be generalizeable to the entire county (Supplemental Table 3-9), although this limitation does not harm internal validity. Additionally, by excluding preterm babies, we have introduced some unknown degree of selection bias because some common cause of IUGR and preterm birth may cause some babies to be born early. However, because nearly 50% of the low weight babies in our

population are also born preterm, including preterm babies in the analysis would essentially be evaluating a very mixed case group, rather than a study of growth restriction. By excluding other adverse birth outcomes also linked to prenatal air pollution exposure, including birth defects,[64] spontaneous abortions,[65] and stillbirth,[66,67] we have induced some degree of selection bias, though the bias is likely downward. Birth defects account for a small percentage of the term low weight births in our population; our study focuses on those low weight births unrelated to birth defects. Finally, we could be missing some potentially important confounders not available through public records. While spatial comparisons are more sensitive to residual confounding by SES-related factors, which tend to vary spatially, temporal comparisons could be sensitive to factors such as temperature and sunlight exposure[68-70]. However, because we observed associations with both spatial comparisons (e.g. unseasonalized LUR metrics) and temporal comparisons (e.g. monitoring station data), it is unlikely that the same residual confounder could bias both these comparisons simultaneously, although both types of comparisons could be biased by separate factors. Comparing results derived from LUR-based and monitoring station-based estimates of air pollution allows us to present stronger evidence of the presence of a real effect.

The major strengths of our study include the use of LUR-modeled exposure estimates for both long-term and pregnancy period-specific air pollution exposures, and a large, diverse population spread over a geographical area with spatial and temporal variations in air pollution concentrations. Additionally, by conducting analyses stratified by monitoring station, we were able to isolate seasonal effects of air pollution, which are less likely to be affected by residual confounding compared to spatial effects, which may

be confounded by SES. With multiple years of birth certificate and air pollution data, we were also able to examine pregnancy period-specific exposures to identify the third trimester as a critical window of exposure for term LBW, consistent with prior studies of traffic-related air pollution, although some studies also identified the first trimester as a critical exposure period.[3,26,71-73].

These analyses provide additional evidence that air toxics may play a role in fetal growth restriction, and highlight the potential for LUR modeling techniques to capture important spatial contrasts in air pollution. Future studies should further explore the utility of air toxics and GIS-based modeling techniques to more accurately characterize traffic-related air pollution exposures across large geographical regions.

FUNDING

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Table 3-1. Pollutant distributions and Pearson's correlation coefficients for entire pregnancy averages for cohort used to evaluate term LBW.

	Pollutant[1]	n	Mean	IQR[2]	SD[3]
LUR U[4]	NO	243425	33 0	11 2	10 5
	NO2	243425	27 8	5 3	4 6
	NOx	243425	60 5	15 5	13 7
LUR S	NO	226869	39 5	19 1	17 0
	NO2	226869	34 1	9 8	7 4
	NOx	226869	73 3	27 4	22 7
Measured	BAP	307267	0 2	0 1	0 1
Pollutants	BGP	307267	0 5	0 3	0 2
	Total PAH	307267	1 4	0 8	0 6
	BENZ	378879	0 9	0 5	0 3
	EBZ	378843	0 3	0 2	0 1
	TOL	378879	2 4	1 0	0 7
	m,p-XYL	365990	1 2	0 5	0 4
	o-XYL	378879	0 4	0 2	0 1
	V	258663	12 3	5 5	3 7
	CO	364146	1 1	0 6	0 4
	NO	338898	41 6	24 1	17 1
	NO_2	338890	34 8	10 4	6 7
	NO_x	338890	76 3	31 2	21 8
	O_3	366191	35 4	8 4	6 1
	PM_{10}	351562	38 4	8 5	5 9
	$PM_{2\,5}$	219975	19 8	4 6	2 8

[1] Pollutant values are expressed in the following units CO ppm, NO, NO_2, NO_x, ppb, PM $\mu g/m^3$, Benzene, Ethyl Benzene, Toluene, m,p-Xylene, o-Xylene, ppbV, BAP10, BGP10, Total PAH, Vanadium, ng/m3

[2] Interquartile range

[3] Standard deviation

[4] Regression models with LUR exposure estimates included only births from the years 2000-2006

Table 3-1, continued

		Pearson Correlation Coefficients																				
		LUR U[6]			LUR S[7]			Measured Pollutants[8]														
	Pollutant[5]	NO	NO_2	NO_x	NO	NO_2	NO_x	BAP	BGP	Total PAH	BENZ	EBZ	TOL	m,p-XYL	o-XYL	V	CO	NO	NO_2	NO_x	O_3	PM_{10}	$PM_{2.5}$
LUR U[9]	NO	1 00																				
	NO2	0 79	1 00																			
	NOx	0 98	0 83	1 00																		
LUR S	NO	0 74	0 60	0 72	1 00																	
	NO2	0 56	0 64	0 58	0 79	1 00																
	NOx	0 70	0 59	0 72	0 97	0 87	1 00															
Measured	BAP	0 00	0 00	0 00	0 46	0 34	0 47	1 00														
Pollutants	BGP	0 00	0 00	0 00	0 53	0 38	0 53	0 86	1 00													
	Total PAH	0 00	0 00	0 00	0 51	0 37	0 51	0 96	0 96	1 00												
	BENZ	0 00	0 01	0 00	0 52	0 60	0 58	0 57	0 60	0 62	1 00											
	EBZ	0 00	0 02	0 00	0 47	0 52	0 52	0 39	0 48	0 46	0 76	1 00										
	TOL	0 00	0 01	0 00	0 48	0 59	0 55	0 45	0 43	0 47	0 85	0 78	1 00									
	m,p-XYL	0 00	0 01	0 00	0 47	0 59	0 54	0 34	0 17	0 29	0 67	0 53	0 86	1 00								
	o-XYL	0 00	0 01	0 00	0 49	0 57	0 55	0 34	0 29	0 35	0 75	0 76	0 94	0 89	1 00							
	V	0 00	0 00	0 00	-0 09	0 00	-0 08	-0 32	-0 57	-0 45	-0 38	-0 29	0 05	0 55	0 19	1 00						
	CO	0 00	0 09	-0 02	0 48	0 60	0 52	0 43	0 61	0 55	0 78	0 60	0 61	0 38	0 51	-0 51	1 00					
	NO	0 03	0 10	0 00	0 53	0 46	0 51	0 51	0 43	0 50	0 52	0 46	0 50	0 45	0 48	-0 09	0 70	1 00				
	NO_2	0 00	0 17	-0 01	0 44	0 72	0 53	0 40	0 51	0 47	0 74	0 61	0 65	0 51	0 56	-0 32	0 84	0 62	1 00			
	NO_x	0 02	0 13	0 00	0 53	0 57	0 55	0 53	0 49	0 53	0 63	0 54	0 59	0 51	0 55	-0 15	0 80	0 97	0 79	1 00		
	O_3	-0 04	0 19	-0 02	-0 36	-0 09	-0 34	-0 49	-0 32	-0 42	-0 19	-0 23	-0 31	-0 34	-0 33	-0 05	-0 06	-0 45	0 12	-0 31	1 00	
	PM_{10}	-0 02	0 11	0 00	0 33	0 58	0 42	0 29	0 33	0 34	0 53	0 48	0 49	0 49	0 43	0 14	0 49	0 15	0 63	0 32	0 29	1 00	
	$PM_{2.5}$	0 01	0 16	0 01	0 34	0 59	0 41	0 30	0 25	0 29	0 56	0 32	0 57	0 66	0 57	0 23	0 78	0 54	0 82	0 66	0 04	0 75	1 00

[5] Pollutant values are expressed in the following units. CO ppm; NO, NO_2, NO_x, ppb, PM $\mu g/m^3$, Benzene, Ethyl Benzene, Toluene, m,p-Xylene, o-Xylene, ppbV, BAP10, BGP10, Total PAH, Vanadium, ng/m3

[6] Unseasonalized LUR estimates.

[7] Seasonalized LUR estimates

[8] Abbreviations: BAP = benzo(a)pyrene, BGP = benzo(g,h,i)perylene, Total PAH = total polycyclic aromatic hydrocarbons (includes Benzo(a)pyrene, Benzo(b)fluoranthene, Benzo(g,h,i)perylene, Benzo(k)fluoranthene, Indeno(1,2,3-cd)pyrene), BENZ=benzene, EBZ=ethyl benzene, TOL=toluene, m,p-XYL = m,p-xylene, o-XYL=o-xylene, V=vanadium

[9] Regression models with LUR exposure estimates included only births from the years 2000-2006

Table 3-2. Pearson's correlation coefficients across pregnancy periods for select pollutants

Pollutant	Period	MEASURED POLLUTANTS				
		1st Trimester	2nd Trimester	3rd Trimester	Entire pregnancy	Last month of pregnancy
NO	1st Trimester	1				
	2nd Trimester	0.10	1			
	3rd Trimester	-0.47	0.16	1		
	Entire pregnancy	0.45	0.79	0.35	1	
	Last month of pregnancy	-0.37	-0.23	0.80	0.06	1
NO_2	1st Trimester	1				
	2nd Trimester	0.52	1			
	3rd Trimester	0.11	0.48	1		
	Entire pregnancy	0.72	0.87	0.69	1	
	Last month of pregnancy	0.11	0.22	0.87	0.51	1
BAP[1]	1st Trimester	1				
	2nd Trimester	-0.16	1			
	3rd Trimester	-0.56	-0.05	1		
	Entire pregnancy	0.27	0.67	0.24	1	
	Last month of pregnancy	-0.41	-0.32	0.68	-0.11	1
Benzene	1st Trimester	1				
	2nd Trimester	0.28	1			
	3rd Trimester	-0.29	0.29	1		
	Entire pregnancy	0.57	0.84	0.47	1	
	Last month of pregnancy	-0.22	-0.08	0.79	0.21	1

Table 3-2, continued

Pollutant	Period	SEASONALIZED LUR-ESTIMATED				
		1st Trimester	2nd Trimester	3rd Trimester	Entire pregnancy	Last month of pregnancy
LUR S[2] NO	1st Trimester	1				
	2nd Trimester	0.13	1			
	3rd Trimester	-0.42	0.12	1		
	Entire pregnancy	0.45	0.77	0.41	1	
	Last month of pregnancy	-0.34	-0.19	0.84	0.18	1
LUR S[3] NO_2	1st Trimester	1				
	2nd Trimester	0.53	1			
	3rd Trimester	0.19	0.54	1		
	Entire pregnancy	0.73	0.88	0.73	1	
	Last month of pregnancy	0.18	0.32	0.87	0.59	1

[1] BAP = benzo(a)pyrene
[2] LUR S = Seasonalized LUR
[3] LUR S = seasonalized LUR

Table 3-3. Demographic Characteristics by Outcome Group and Crude Odds Ratios (95% CI) for Term LBW

Parameter	Term LBW Cases (N=8,181) n (%) or mean (SD)	Non-Cases (N=370,922) n (%) or mean (SD)	Crude Term LBW OR (95% CI)
Gestational age (days) mean (SD)	273.6 (10.9)	278.7 (10.3)	--
Birth weight (g) mean (SD)	2288.5 (241.0)	3429.4 (429.7)	--
Infant gender			
Female	4653 (56.9)	182249 (49.1)	1.37 (1.31, 1.43)
Male	3528 (43.1)	188673 (50.9)	1.00
Missing			
Maternal age (years)			
<20	1317 (16.1)	42083 (11.4)	1.30 (1.22, 1.39)
20-24	2252 (27.5)	93655 (25.3)	0.78 (0.73, 0.83)
25-29	1920 (23.5)	102654 (27.7)	1.00
30-34	1557 (19.0)	81809 (22.1)	0.79 (0.74, 0.85)
≥35	1135 (13.9)	50721 (13.7)	0.93 (0.87, 1.00)
Missing			
Maternal race/ethnicity			
Hispanic	5341 (65.3)	259561 (70.0)	1.25 (1.16, 1.35)
White, non-Hispanic	825 (10.1)	50131 (13.5)	1.00
African American	865 (10.6)	20969 (5.7)	2.51 (2.28, 2.76)
Asian	586 (7.2)	22895 (6.2)	1.56 (1.40, 1.73)
Other[2]	549 (6.7)	16698 (4.5)	2.00 (1.79, 2.23)
Missing	15 (0.2)	668 (0.2)	
Maternal education (years)			
≤8	2128 (26.0)	97242 (26.2)	0.95 (0.89, 1.01)
9-11	1969 (24.1)	80941 (21.8)	1.06 (0.99, 1.12)
12	2080 (25.4)	90215 (24.3)	1.00
13-15	1106 (13.5)	53663 (14.5)	0.89 (0.83, 0.96)
≥16	811 (9.9)	45861 (12.4)	0.77 (0.71, 0.83)
Missing	87 (1.1)	3000 (0.8)	
Parity			
0	3931 (48.1)	140832 (38.0)	1.51 (1.45, 1.58)
1 or more	4245 (51.9)	230006 (62.0)	1.00
Missing	5 (0.1)	84 (0.0)	
Prenatal Care			
No prenatal care or started after 1st trimester	1305 (16.0)	48066 (13.0)	1.28 (1.21, 1.36)
Started in first trimester	6819 (83.4)	321411 (86.7)	1.00
Missing	57 (0.7)	1445 (0.4)	
Mother's Birthplace (U.S. vs outside U.S.)			
U.S. Born	3090 (37.8)	132748 (35.8)	1.00

Parameter	Term LBW Cases (N=8,181) n (%) or mean (SD)	Non-Cases (N=370,922) n (%) or mean (SD)	Crude Term LBW OR (95% CI)
Foreign Born	5080 (62.1)	237399 (64.0)	0.92 (0.88, 0.96)
Missing	11 (0.1)	775 (0.2)	
Mother's Birthplace			
U.S.	3090 (37.8)	132748 (35.8)	1.00
Mexico	2737 (33.5)	141523 (38.2)	0.83 (0.79, 0.88)
Other outside U.S. (includes Puerto Rico)	2343 (28.6)	95876 (25.9)	1.05 (0.99, 1.11)
Missing	11 (0.1)	775 (0.2)	
Primary Payment for Prenatal Care			
Private, HMO, Blue Cross-Blue Shield	2493 (30.5)	138183 (37.3)	1.00
Medicare, Medi-Cal, government, other non-government programs	5401 (66.0)	222329 (59.9)	1.35 (1.28, 1.41)
No prenatal care, Self pay, no charge, medically indigent, other	279 (3.4)	10152 (2.7)	1.52 (1.34, 1.73)
Missing	8 (0.1)	258 (0.1)	
Census-Based SES Index (quintiles)			
Q1	4901 (59.9)	206567 (55.7)	1.00
Q2	1669 (20.4)	78237 (21.1)	0.90 (0.85, 0.95)
Q3	924 (11.3)	45960 (12.4)	0.85 (0.79, 0.91)
Q4	489 (6.0)	28184 (7.6)	0.73 (0.67, 0.80)
Q5	197 (2.4)	11880 (3.2)	0.70 (0.61, 0.81)
Missing	1 (0.01)	94 (0.03)	

(1) Includes 379,103 births during January 1, 1995 to December 31, 2006 to women residing within 5 miles of a CARB air toxics monitoring station; excludes preterm births.
(2) Includes Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, Other (specified).

Table 3-4. Adjusted Odds Ratios and 95% Confidence Intervals for term LBW for seasonalized LUR exposure estimates, comparing across pregnancy periods for births in the years 2000-2006 only. Odds ratios and confidence intervals are calculated per 10ppb for each pollutant. Models are adjusted for maternal age, race, education, parity, gestational age and gestational age squared.

		Seasonalized LUR exposure estimate		Monitoring station estimate	
	Pollutant	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)
ENTIRE PREGNANCY	NO	4619, 205402	1.03 (1.01, 1.05)	4619, 205402	1.02 (1.00, 1.04)
	NO_2	4619, 205402	1.07 (1.03, 1.11)	4619, 205402	1.05 (1.00, 1.11)
	NO_x	4619, 205402	1.02 (1.01, 1.03)	4619, 205402	1.02 (1.00, 1.03)
FIRST TRIMESTER	NO	4778, 213096	1.00 (1.00, 1.01)	4778, 213096	1.00 (0.99, 1.01)
	NO_2	4778, 213096	1.03 (1.00, 1.06)	4778, 213096	1.01 (0.98, 1.05)
	NO_x	4778, 213096	1.00 (1.00, 1.01)	4778, 213096	1.00 (0.99, 1.01)
SECOND TRIMESTER	NO	4769, 212727	1.01 (1.00, 1.02)	4769, 212727	1.01 (1.00, 1.02)
	NO_2	4769, 212727	1.04 (1.01, 1.07)	4769, 212727	1.03 (0.99, 1.07)
	NO_x	4769, 212727	1.01 (1.00, 1.02)	4769, 212727	1.01 (1.00, 1.01)
THIRD TRIMESTER	NO	4740, 211077	1.02 (1.01, 1.03)	4740, 211077	1.01 (1.00, 1.02)
	NO_2	4740, 211077	1.05 (1.02, 1.09)	4740, 211077	1.04 (1.00, 1.08)
	NO_x	4740, 211077	1.01 (1.01, 1.02)	4740, 211077	1.01 (1.00, 1.02)
LAST MONTH OF PREGNANCY	NO	4823, 214918	1.01 (1.00, 1.02)	4823, 214918	1.01 (1.00, 1.02)
	NO_2	4823, 214918	1.05 (1.02, 1.08)	4823, 214918	1.04 (1.00, 1.07)
	NO_x	4823, 214918	1.01 (1.00, 1.02)	4823, 214918	1.01 (1.00, 1.02)

Table 3-5. Adjusted Odds Ratios and 95% Confidence Intervals for term LBW models unstratified, and stratified by station. Exposure estimates are scaled by the interquartile range for each pollutant from the unstratified dataset. Models are adjusted for maternal age, race, education, parity, gestational age and gestational age squared.

	Overall model (All stations)		Stratified by station North Long Beach	
	N (cases, non-cases)	N (cases, non-cases)	N (cases, non-cases)	OR (95% CI)
UNSEASONALIZED LUR				
NO	4837, 215897	1363, 58175	1363, 58175	1.05 (0.98, 1.13)
NO_2	4837, 215897	1363, 58175	1363, 58175	1.09 (0.98, 1.21)
NO_x	4837, 215897	1363, 58175	1363, 58175	1.05 (0.98, 1.13)
THIRD TRIMESTER				
LUR S NO	4740, 211077	1356, 57924	1356, 57924	1.05 (0.98, 1.13)
LUR S NO_2	4740, 211077	1356, 57924	1356, 57924	1.05 (0.98, 1.12)
LUR S NO_x	4740, 211077	1356, 57924	1356, 57924	1.04 (0.98, 1.11)
benzo(a)pyrene	6817, 312183	1770, 77677	1770, 77677	1.02 (0.96, 1.08)
benzo(g,h,i)perylene	6817, 312183	1770, 77677	1770, 77677	1.01 (0.95, 1.07)
Total PAH	6817, 312183	1770, 77677	1770, 77677	1.02 (0.96, 1.08)
Benzene	8083, 367468	2133, 93249	2133, 93249	1.02 (0.95, 1.09)
Ethyl benzene	8083, 367456	2133, 93249	2133, 93249	1.01 (0.95, 1.08)
m,p-Xylene	8083, 367466	2133, 93249	2133, 93249	1.04 (0.98, 1.10)
o-Xylene	8083, 367468	2133, 93249	2133, 93249	1.05 (0.99, 1.12)
Toluene	8083, 367468	2133, 93249	2133, 93249	1.03 (0.96, 1.09)
Vanadium	5443, 250773	1371, 60528	1371, 60528	1.03 (0.97, 1.09)
CO	7944, 361034	2066, 89709	2066, 89709	1.03 (0.96, 1.11)
NO	7616, 345034	2066, 89709	2066, 89709	1.04 (0.96, 1.12)
NO_2	7616, 345030	2066, 89709	2066, 89709	1.03 (0.96, 1.10)
NO_x	7616, 345030	2066, 89709	2066, 89709	1.03 (0.96, 1.11)
O_3	7956, 361524	2066, 89710	2066, 89710	0.96 (0.86, 1.07)
PM_{10}	7845, 354789	2062, 89477	2062, 89477	1.04 (0.97, 1.10)
$PM_{2.5}$	5233, 235037	1509, 65323	1509, 65323	1.03 (0.97, 1.10)

Table 3-5, continued

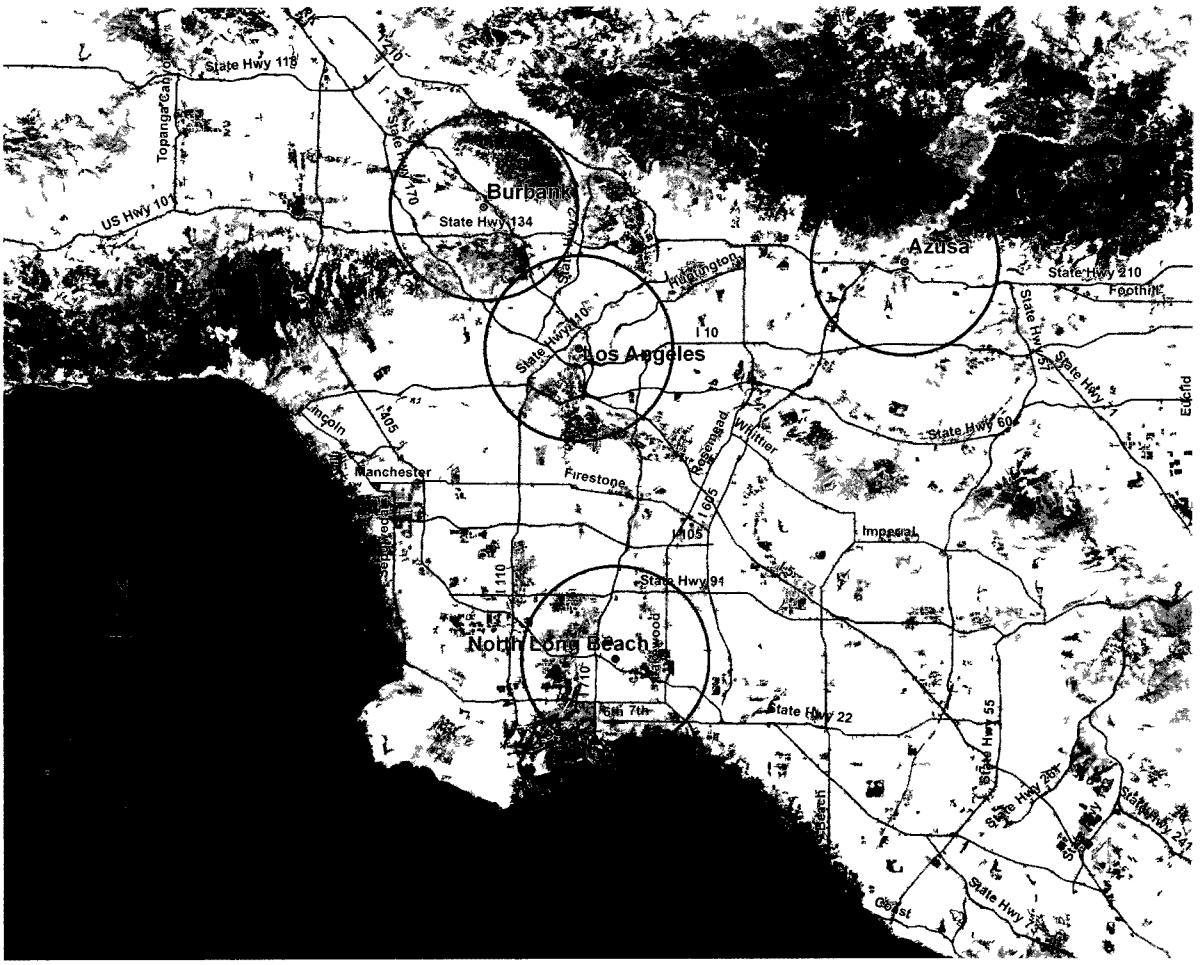
	Stratified by Station					
	Azusa		Burbank		Downtown LA	
	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)
UNSEASONALIZED LUR						
NO	507, 26489	0.95 (0.82, 1.09)	582, 31422	1.03 (0.93, 1.14)	2385, 99811	1.07 (1.04, 1.11)
NO_2	507, 26489	0.89 (0.77, 1.03)	582, 31422	1.02 (0.91, 1.13)	2385, 99811	1.09 (1.04, 1.13)
NO_x	507, 26489	0.95 (0.82, 1.09)	582, 31422	1.02 (0.91, 1.13)	2385, 99811	1.08 (1.04, 1.12)
THIRD TRIMESTER						
LUR S NO	506, 26380	1.13 (1.05, 0.88)	571, 30572	0.88 (1.26, 1.07)	2307, 96201	1.07 (0.97, 1.18)
LUR S NO_2	506, 26380	1.12 (1.03, 0.90)	571, 30572	0.90 (1.18, 1.04)	2307, 96201	1.04 (0.92, 1.18)

LUR S NO_x	506, 26380	1.11 (1.07, 0.88)	571, 30572	0.88 (1.30, 1.07)	2307, 96201	1.07 (0.96, 1.19)
BAP[a]	740, 39745	0.98 (0.90, 1.07)	851, 45823	1.03 (0.95, 1.11)	3456, 148938	1.01 (0.98, 1.05)
BGP[b]	740, 39745	0.97 (0.89, 1.06)	851, 45823	1.07 (0.99, 1.15)	3456, 148938	1.01 (0.97, 1.05)
Total PAH	740, 39745	0.97 (0.89, 1.06)	851, 45823	1.05 (0.97, 1.14)	3456, 148938	1.01 (0.97, 1.05)
Benzene	873, 46507	0.99 (0.89, 1.09)	1019, 53850	1.10 (1.01, 1.20)	4058, 173862	1.04 (0.99, 1.09)
Ethyl benzene	873, 46507	1.04 (0.95, 1.14)	1019, 53843	1.04 (0.96, 1.13)	4058, 173857	1.01 (0.97, 1.05)
m,p-Xylene	873, 46507	0.98 (0.90, 1.07)	1019, 53849	1.05 (0.97, 1.14)	4058, 173861	1.03 (0.99, 1.08)
o-Xylene	873, 46507	1.00 (0.91, 1.10)	1019, 53850	1.06 (0.98, 1.16)	4058, 173862	1.03 (0.99, 1.08)
Toluene	873, 46507	1.01 (0.92, 1.11)	1019, 53850	1.07 (0.99, 1.17)	4058, 173862	1.04 (0.99, 1.08)
Vanadium	598, 32588	1.03 (0.94, 1.12)	690, 36884	0.98 (0.90, 1.07)	2784, 120773	0.99 (0.95, 1.03)
CO	873, 46507	1.06 (0.91, 1.24)	1007, 53397	1.07 (1.00, 1.15)	3998, 171421	1.04 (1.00, 1.08)
NO	873, 46507	1.18 (0.78, 1.77)	953, 50052	1.05 (0.97, 1.15)	3724, 158766	1.03 (0.99, 1.07)
NO_2	873, 46507	1.02 (0.93, 1.11)	953, 50048	1.11 (1.00, 1.23)	3724, 158766	1.05 (1.00, 1.11)
NO_x	873, 46507	1.09 (0.85, 1.39)	953, 50048	1.07 (0.98, 1.17)	3724, 158766	1.04 (0.99, 1.08)
O_3	873, 46507	1.00 (0.92, 1.08)	1019, 53886	0.97 (0.89, 1.06)	3998, 171421	0.99 (0.94, 1.04)
PM_{10}	816, 42942	1.04 (0.98, 1.11)	968, 51325	1.07 (0.97, 1.18)	3999, 171045	1.05 (1.01, 1.10)
$PM_{2.5}$	551, 28564	1.07 (0.95, 1.21)	559, 29746	1.01 (0.91, 1.13)	2614, 111404	1.07 (1.01, 1.14)

[a] BAP=benzo(a)pyrene

[b] BGP = benzo(g,h,i)perylene

Figure 3-1. CARB air toxics monitoring stations in the Los Angeles Basin



SUPPLEMENTAL MATERIAL FOR CHAPTER 3

Comparing GIS-based and air toxics exposure measures of traffic-related pollution: a study of term low birth weight in Los Angeles County, California

Table 3-6. Supplemental table. Geocoding quality flags for Los Angeles County, California births from 1995-2006, excluding births with recorded defects, missing or extreme gestational ages, missing or extreme birth weights, and multiple gestations. Addresses that were not geocodeable were excluded (n=2,612).

	Quality flag	N (%)
Good quality geocodes	Exact parcel centroid	694,154 (45.5%)
	Uniform lot interpolation	300,845 (19.7%)
	Address range interpolation	424,012 (27.8%)
Poorer quality gecodes	Zip code tabulation area centroid	23,354 (6.2%)
	City centroid	116, (<0.1%)
	County subdivision centroid	3 (<0.1%)

Table 3-7. Supplemental table. Exclusion criteria used when estimating pregnancy period specific air pollution exposure metrics.

Pollutant	Data Availability	Criteria
Air Toxics	24-hour averages, every 12 days	Criteria for pregnancy periods: At least 1 reading for each full month in a given period (trimester or entire pregnancy) as well as 1 reading during the last 30 days of the pregnancy period.
CO	hourly	Criteria for hourly measurements: At least 50% of hourly values available per 24-hr period and at least 50% of hourly values available from 6am-6pm. If sufficient data were available, a daily (24-hour) average was generated based on the hourly data. Criteria for pregnancy periods: We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
NO, NO_2, NO_x	hourly	Criteria for hourly measurements: At least 50% of hourly values available per 24-hr period and at least 50% of hourly values available from 8am-8pm. Criteria for pregnancy periods: We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
O_3 (10am-6pm)	hourly	Criteria for hourly measurements: At least 50% of hourly values available from 10am-6pm. Criteria for pregnancy periods:

		We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
PM_{10}	24-hour average, every 6 days	We required 3 or more values to be available per each full pregnancy month and during the last 30 days of pregnancy.
$PM_{2.5}$	24-hour average, every 3 days	We required 5 or more values to be available per each full pregnancy month and during the last 30 days of pregnancy.

Table 3-8. Supplemental table. Adjusted Odds Ratios and 95% Confidence Intervals for term LBW models using exposure averages for the last month of pregnancy. Exposure estimates are scaled by the interquartile range for each pollutant from the unstratified dataset. Models are adjusted for maternal age, race, education, parity, gestational age and gestational age squared.

	N (cases, non-cases)	OR (95% CI)
LUR S NO	4823, 214918	1.05 (1.02, 1.08)
LUR S NO_2	4823, 214918	1.06 (1.02, 1.10)
LUR S NO_x	4823, 214918	1.05 (1.02, 1.09)
benzo(a)pyrene	6817, 312239	1.02 (1.00, 1.04)
benzo(g,h,i)perylene	6817, 312239	1.02 (1.00, 1.04)
Total PAH	6817, 312239	1.02 (1.01, 1.04)
Benzene	8084, 367521	1.05 (1.02, 1.08)
Ethyl benzene	8084, 367516	1.03 (1.01, 1.06)
m,p-Xylene	8084, 367521	1.04 (1.01, 1.07)
o-Xylene	8084, 367521	1.04 (1.01, 1.06)
Toluene	8084, 367521	1.04 (1.01, 1.06)
Vanadium	5443, 250782	1.00 (0.97, 1.02)
CO	8016, 363961	1.06 (1.03, 1.09)
NO	7821, 354213	1.06 (1.03, 1.08)
NO_2	7821, 354209	1.05 (1.02, 1.09)
NO_x	7821, 354209	1.06 (1.03, 1.09)
O_3	8028, 364281	0.97 (0.93, 1.00)
PM_{10}	7994, 362076	1.02 (1.00, 1.05)
$PM_{2.5}$	5375, 243224	1.02 (0.99, 1.06)

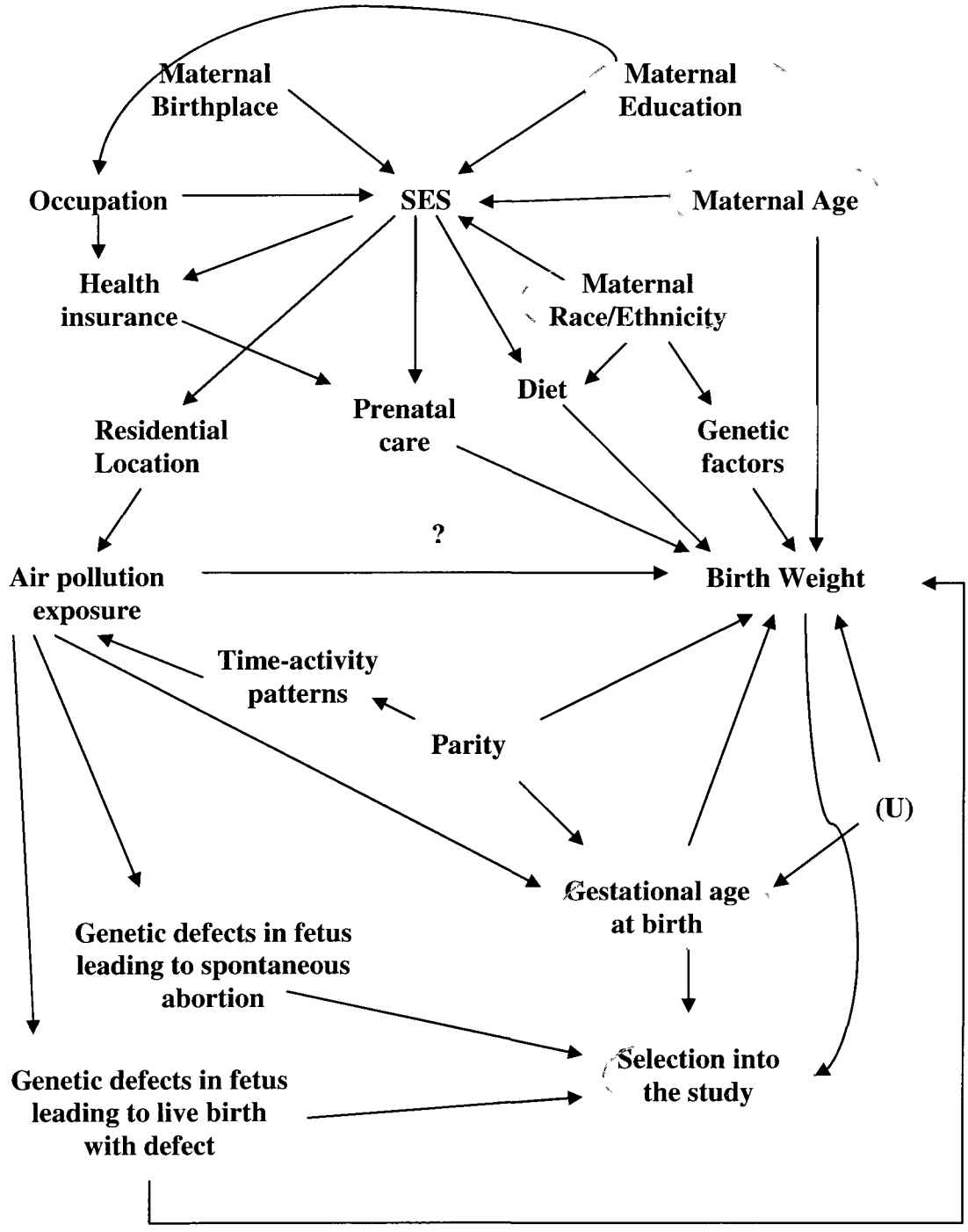
Table 3-9. Supplemental table. Demographic characteristics (n, %) of term LBW cohort compared to all term births in LA County during 1/1/1995 to 12/31/2006. (excluding births with recorded abnormalities, extreme or missing gestational age or birth weight data, and multiple births)

Parameter	All LA County births (N= 1,393,243)	Geocoded births (N= 1,390,993)	Geocoded births within 5 mi of a CARB station (N=379,103)
Gestational age (days) (mean, SD)	278.7 ± 10.4	278.7 ± 10.4	278.6 ± 10.3
Birth weight (g) (mean, SD)	3410.5 ± 457.8	3410.5 ± 457.8	3404.8 ± 457.6
Infant gender			
Female	686819 (49.3)	685711 (49.3)	186902 (49.3)
Male	706421 (50.7)	705279 (50.7)	192201 (50.7)
Missing	3 (0.0)	3 (0.0)	
Maternal age (years)			
<20	146879 (10.5)	146621 (10.5)	43400 (11.5)
20-24	325429 (23.4)	324867 (23.4)	95907 (25.3)
25-29	372727 (26.8)	372159 (26.8)	104574 (27.6)
30-34	330440 (23.7)	329941 (23.7)	83366 (22.0)
≥35	217631 (15.6)	217268 (15.6)	51856 (13.7)
Missing	137 (0.0)	137 (0.0)	
Maternal race/ethnicity			
Hispanic	871317 (62.5)	870020 (62.6)	264902 (69.9)
White, non-Hispanic	255312 (18.3)	254740 (18.3)	50956 (13.4)
African American	109964 (7.9)	109807 (7.9)	21834 (5.8)
Asian	96814 (7.0)	96722 (7.0)	23481 (6.2)
Other[a]	55833 (4.0)	55725 (4.0)	17247 (4.6)
Missing	4003 (0.3)	3979 (0.3)	683 (0.2)
Maternal education (years)			
≤8	316892 (22.7)	316253 (22.7)	99370 (26.2)
9-11	269774 (19.4)	269367 (19.4)	82910 (21.9)
12	348885 (25.0)	348387 (25.1)	92295 (24.4)
13-15	212541 (15.3)	212198 (15.3)	54769 (14.5)
≥16	231874 (16.6)	231574 (16.7)	46672 (12.3)
Missing	13277 (1.0)	13214 (1.0)	3087 (0.8)
Parity			
0	539865 (38.8)	538841 (38.7)	144763 (38.2)
1 or more	852959 (61.2)	851736 (61.2)	234251 (61.8)
Missing	419 (0.0)	416 (0.0)	89 (0.0)
Prenatal Care			
No prenatal care or started after 1st trimester	165464 (11.9)	165139 (11.9)	49371 (13.0)
Started in first trimester	1218699 (87.5)	1216817 (87.5)	328230 (86.6)
Missing	1218699 (87.5)	9037 (0.7)	1502 (0.4)
Mother's Birthplace (U.S. vs outside U.S.)			
U.S. Born	590578 (42.4)	589519 (42.4)	135838 (35.8)
Foreign Born	800677 (57.5)	799490 (57.5)	242479 (64.0)

Parameter	All LA County births (N= 1,393,243)	Geocoded births (N= 1,390,993)	Geocoded births within 5 mi of a CARB station (N=379,103)
Missing	1988 (0.1)	1984 (0.1)	786 (0.2)
Mother's Birthplace			
U.S.	590578 (42.4)	589519 (42.4)	135838 (35.8)
Mexico	474243 (34.0)	473592 (34.1)	144260 (38.1)
Other outside U.S. (includes Puerto Rico)	326434 (23.4)	325898 (23.4)	98219 (25.9)
Missing	1988 (0.1)	1984 (0.1)	786 (0.2)
Primary Payment for Prenatal Care			
Private insurance, HMO, Blue Cross-Blue Shield	621371 (44.6)	620504 (44.6)	140676 (37.1)
Medicare, Medi-Cal, government insurance programs, other non-government insurance programs	724790 (52.0)	723521 (52.0)	227730 (60.1)
No prenatal care, Self pay, no charge, medically indigent, other	45358 (3.3)	45252 (3.3)	10431 (2.8)
Missing	1724 (0.1)	1716 (0.1)	266 (0.1)

[a] Includes Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, Other (specified).

Figure 3-2. Supplemental figure. Directed acyclic graph showing the hypothesized relationships among key variables in the study.



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Chapter 4

Use of ambient air toxics and LUR-modeling approaches to examine air pollution effects on preterm birth in Los Angeles County, California

BACKGROUND

Prenatal exposure to air pollution has been associated with increased risk of preterm birth in studies using ambient criteria pollutant data, but there is no consensus on the biological mechanisms or specific pollutants causing these effects.[1-5] Studies examining air toxics including polycyclic aromatic hydrocarbons (PAHs) and benzene suggest these pollutants may play a role in fetal development and early parturition.[6-11] However, most existing studies of birth outcomes have assessed only ambient criteria pollutants, such as carbon monoxide (CO) or particulate matter less than 2.5 μg in aerodynamic diameter ($PM_{2.5}$) due to commonly available air monitoring station data used for regulatory purposes. Criteria pollutants may act as markers of traffic exhaust rather than be causative agents of adverse birth outcomes themselves. To date, due to the limited availability of routine air toxics monitoring data, few population-based birth outcomes studies have examined association with PAHs, benzene, and other air toxics.[10,12-17]

Another major criticism of ambient criteria pollutant studies is their inability to capture fine spatial variation in primary traffic exhaust pollution – a limitation that newer GIS-based methods, such as land use-based regression (LUR) modeling, have tried to address. LUR methods employ short-term monitoring of a small number of traffic markers on a fine spatial scale, and incorporate data on traffic counts, meteorology, and other pollution sources.[18-20] The resulting prediction surfaces provide a detailed spatial map of air pollution, representing average pollution concentrations over time. To study

short or medium-term exposures that are relevant to pregnancy outcome studies, such as months or pregnancy trimesters, LUR models need to be "seasonalized" to reflect temporal variations in air pollution.[21,22] LUR models are only beginning to be used in pregnancy outcomes studies, with only five previous studies that have used LUR modeling methods to examine associations with preterm birth.[23-26]

One of these studies was recently conducted by our research group and used LUR modeled exposure estimates along with air toxics monitoring data from the Multiple Air Toxics Exposure Study (MATES III). The study included births spanning 22 months in 2004-2006 to correspond to the dates of available MATES monitoring data. While our MATES-based study was able to evaluate a large number of air toxics including source-specific $PM_{2.5}$ estimates from a Chemical Mass Balance model, and included many LA neighborhoods in the study, we could not conduct stratified analyses or evaluate risk of very preterm birth (defined as <32 weeks completed gestation) because of the smaller sample size available.

The present study of preterm birth in LA County serves to compliment our previous work, and uses ambient air toxics and criteria pollutant monitoring data provided by a small network of monitors managed by the California Air Resources Board (CARB) to estimate air toxics exposures across a very large number of births spanning 12 years (1995-2006). Additionally, we use a LUR model based on NO, NO_2, and NO_x measurements in the Los Angeles air basin to represent fine spatial variations in longer-term traffic-related exposures, and a "seasonalized" version that incorporates temporal variations into the modeled estimates. With this unique dataset, we evaluate preterm birth and very preterm birth risk in the overall population and identify critical time periods of

exposure during pregnancy. We also conduct stratified analyses to identify susceptible subgroups within the population and to evaluate effects of temporal fluctuations in air toxics independent from spatial variations, which are more susceptible to spatial confounders such as socioeconomic status (SES).

METHODS

Birth certificate data and outcome assessment

We used electronic birth certificate data from the State of California to identify women who gave birth between 1/1/1995 to 12/31/2006 while residing in Los Angeles County, California (n= 1,745,754). From these birth certificates, we obtained the mother's address at the time of birth, as well as information about maternal age, race/ethnicity, education, parity, timing of initiation of prenatal care, payment source for prenatal care, baby's gestational age at birth, birth weight, sex, date of birth, other demographic information and information about complications of pregnancy and delivery. We used the gestational age information to identify preterm babies (<37 completed gestational weeks) and very preterm babies (<32 completed gestational weeks). We excluded births with recorded defects (n=85,114) because we wished to study biological pathways leading to preterm birth independent of birth defects. We also excluded records with missing or implausible data for our case definition, including missing (n=81,072) or extreme gestational ages (<140 days, or >320 days) (n=19,139) or birth weights (<500 g, or >5,000 g) (n=3,125) likely due to recording errors. Multiple gestations (n=32,425) were also excluded, because the biological pathways leading to preterm birth in multiple gestations are likely to differ from singleton births.

All addresses were geocoded using the University of Southern California GIS Research Laboratory geocoding engine, and 2,612 non-geocodable addresses were excluded.[27] Geocoding quality flags are shown in Supplement Table 4-6 of our related manuscript.[28] While the majority of the addresses were matched to high quality geocodes, <7% of the addresses matched only lower quality geocodes (centroids for zip code, city, and county subdivision); excluding these poorer quality geocoded addresses did not change our results. Address locations for all geocoded addresses (n=1,522,627) were mapped in ESRI ArcGIS software, and overlaid with the geocoded CARB air toxics station locations in LA County to restrict the dataset to addresses ≤5 miles (8km) of a CARB air toxics monitoring station (n=415,531, 27.3%). This radius was selected to balance sample size needs and the potential for increased exposure misclassification with greater distances from stations.

We used a case-control risk-set approach, matching on gestational age. For each preterm or very preterm case, we randomly selected 10 controls that were still *in utero* at the gestational age of the case's birth. Accordingly, some preterm babies were selected as controls for cases who were born at an earlier gestational age. The risk-set control sampling allowed us to draw from the most comparable population at risk available in our data.

Exposure assessment

The CARB agency maintains four air toxics monitoring stations in Los Angeles County. Three stations were active over the entire study period (Downtown LA, Burbank, and north Long Beach), while one station provided measurements from 2000-

2006 only (Azusa) (Figure 4-1). Measurements for benzene, toluene, ethyl benzene, and xylenes (BTEX) were available for the entire study period, but PAH measurements ceased in December 2004, and vanadium measurements in late February 2003. $PM_{2.5}$ measurements began in January 1999, and there are several months of missing data within our study period for the Burbank station (missing 1/1/2000-3/19/2000 and 5/18/2000-7/11/2000). These stations also collected criteria pollutant data.

Exposure estimates were created for the 1st, 2nd and 3rd trimester, and the last 30 days before birth. For criteria air pollutants, averages were created for CO, NO, NO_2, NO_x, ozone (10am-6pm), PM_{10}, and $PM_{2.5}$. For the gaseous pollutants (hourly data), 24-hour averages were first calculated and then averaged over a pregnancy period. For air toxics, averages were created for two PAHs previously suggested to have important health effects (benzo(a)pyrene (BAP) and benzo(g,h,i)perylene (BGP)), total PAHs (BAP, BGP, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenz(a,h)anthracene, and indeno(1,2,3-cd) pyrene), benzene, ethyl benzene, m,p-xylene, o-xylene, toluene, and vanadium. We applied exclusion criteria per pollutant based on having >50% of the available measurements over the pregnancy period (see Supplement Table 4-6 in our related manuscript for a detailed description of the completeness criteria[28]).

Most subjects lived within 5 miles (8 km) of only one CARB air toxics station (99.1%). However, there were some subjects who lived within 5 miles (8 km) of both the Burbank and Downtown LA stations. For these subjects, we created 24-hour averages for each day with sufficient air pollution data (from one or both stations), and then averaged these daily averages, weighted by the inverse of the distance to the station. If

neither station met the completeness criteria, the value for the exposure period was set to missing.

Exposure estimates for controls matched to preterm cases were based on the gestational age cutoffs of the matched case. For example, we calculated the entire pregnancy average for a case with a gestational age of 250 days and a matched control with a gestational age of 270 days over the time period from day 1 through 250 of each pregnancy.

LUR model and seasonalization

We estimated traffic air pollution exposures using land use-based regression (LUR) models we previously developed for the LA Basin.[29] Because the LUR models were based on measurement data we collected in 2006-2007, we restricted the LUR analyses to births occurring in the years 2000-2006 only. The LUR model was developed based on a very large number of monitoring locations throughout LA County, and was able to explain 81%, 86% and 85% of the variance in measured NO, NO_2 and NO_x concentrations, respectively.[29]

We overlaid the geocoded residential addresses from the birth certificate with the LUR surfaces to assign estimated exposures. The LUR models were developed to assess long-term exposures and most closely approximate annual average concentrations.[29] Therefore, in addition to using the LUR annual average estimates ("unseasonalized estimates"), we also created "seasonalized" LUR measures using measurement data from the air monitoring station(s) closest to each woman's home address. Specifically, the LUR estimates were adjusted (multiplied) to generate pregnancy-month specific LUR

values as follows (using first pregnancy month NO_x as an example): First month seasonalized NO_x average = LUR NO_x * (first month average NO_x/2006 annual average NO_x). The "seasonalized" pregnancy month LUR values were then averaged over the pregnancy periods of interest.

We applied the same hourly and daily exclusion criteria as described above when generating the pregnancy month scaling factors for NO, NO_2 and NO_x. The scaling factors for women within 5 miles (8 km) of two stations were based on a weighted average of values from both stations, again using the same method as above for criteria pollutant exposures.

Statistical Analysis

All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). We plotted pollutant measures to examine trends over time and across the four monitoring stations. Pearson's correlation coefficients were used to assess collinearity across measured and modeled pollutant estimates for each pregnancy period.

Conditional logistic regression methods that accounted for matching on gestational age were used to estimate increases in risk of preterm birth and very preterm birth per unit or interquartile range (IQR) increase in pregnancy-period exhaust toxin exposures. We adjusted for several potential confounders that were important in our previous studies of air pollution and birth outcomes[3]— maternal age, race, education, and parity (Supplement Figure 4-2). We further examined changes in air pollution effect estimates with adjustment for other variables, including mother's birthplace, timing of initiation of prenatal care, payment source for prenatal care (as an SES indicator), and a

previously-developed metric of socioeconomic status (SES) based on Census block group data, where the block groups were categorized into quintiles based on the SES score.[30,31] Given that the birthplace, prenatal care, and SES variables did not change the air pollution effect estimates by more than 5% and did not appear to improve the model fit substantially, the final models were adjusted for maternal age, race, education, and parity. See Supplement Figure 4-2 for a diagram of the relationships among key variables in the study.

To examine possible effect measure modification, we additionally conducted stratified analysis by maternal race/ethnicity for the analysis of preterm birth only. We additionally adjusted for the Census-based SES variable in these stratified models.

Two-pollutant logistic regression models were applied to vanadium, BAP, benzene, seasonalized and unseasonalized LUR measures across all pregnancy periods examined. The co-pollutants considered were CO, NO, NO_2, NO_x, $PM_{2.5}$, BAP, benzene, and vanadium, and seasonalized LUR-estimated NO, NO_2, and NO_x, excluding pairs of pollutants that covaried strongly within the pregnancy period ($|r| \geq 0.7$ excluded).

RESULTS

Seasonal trends and correlations across air pollutants

All measured air toxics except for vanadium showed strong seasonal trends, with peak levels occurring in the winter. Benzene levels markedly decreased over the 12 year study period by about 65%; PAH levels also decreased over the period (about 40%). On average, the highest VOC levels were measured at the Burbank and Downtown LA stations, while PAHs were highest in Burbank, with Downtown LA and North Long

Beach measuring slightly lower levels. Vanadium levels were highest on average in North Long Beach. The majority of women lived within 5 miles (8 km) of only one monitoring station, but 3785 women (0.9% of n=415,531 total) lived within 5 miles (8 km) of both the Burbank and Downtown LA stations.

Seasonalized LUR-based exposure estimates were moderately positively correlated with all measured air toxics (r~0.34-0.60) except for vanadium, most likely because these air toxics were selected to be included in our study precisely because they are important components of traffic exhaust – a major contributor to air pollution in the LA basin.[32] Although vanadium is found in traffic exhaust, industrial sources and shipping emissions may be more significant contributors.[33] Unseasonalized LUR exposure estimates correlated only with seasonalized LUR estimates (r~0.45-0.75), and not with any of the measured air toxics (Table 4-1). Measured toxics were strongly correlated within each pollutant class (PAHs, BTEX), but vanadium showed moderate negative correlations with PAHs, benzene, and ethyl benzene (r ranging from -0.29 to -0.57), and positive correlations with m,p-xylene (r=0.55). Benzene and PAHs correlated strongly with CO, and had moderate to strong correlations with NO, NO_2 and NO_x. Correlations across all pollutants evaluated are shown in Table 4-1.

Pollutant estimates were correlated across pregnancy periods (Table 4-2). Both measured and LUR-estimated pollutants showed strong positive correlations between 2nd trimester and entire pregnancy averages (r~0.75-0.92). Entire pregnancy averages were moderately to strongly correlated with first trimester averages across all pollutants (r~0.44-0.79), and to last month of pregnancy averages of NO_2 and BTEX (r~0.37-0.59). PAHs, NO, and NO_x showed moderate negative correlations between 1st trimester and

last month of pregnancy averages (r~-0.31 to -0.45), while NO_2 and BTEX pollutants showed very weak correlations between these periods (r~0.002-0.22).

Air Pollution and Preterm Birth

The analysis dataset included n=36,428 preterm births, and n=364,280 matched controls. The dataset restricting to year 2000-2006 births (for the analyses using LUR exposure estimates) contained n=20,813 preterm cases, and n=122,215 matched controls. The cohort of pregnant women that was the source for cases and controls (n=415,531) is predominantly Hispanic (70.2%), 72.6% of whom were born outside of the United States (US), mostly in Mexico (Table 4-3). About half of the mothers received less than a high school education, and 62.1% were having their second or subsequent baby. The majority of women had prenatal care starting in the first trimester (86.5%), and government-based insurance to pay for prenatal care services (60.6%).

Preterm births in our dataset had a mean gestational age (GA) of 244.1 days (standard deviation (SD) = 16.9 days) (Table 4-3). Higher risk of preterm birth was observed for mothers who were in the youngest (<20 years) and oldest (≥35 years) age groups, mothers with fewer years of education, women without or with late prenatal care, women with Medical or other government-sponsored insurance programs or had no insurance, multiparous mothers, and mothers born outside the US. In univariate models, African American mothers had the highest risk of preterm birth (crude odds ratio (cOR) (95% confidence interval (CI) =1.80 (1.71, 1.89)) compared to non-Hispanic whites. Hispanic (cOR (95% CI)=1.41 (1.37, 1.47)) and Asian mothers (cOR (95%CI) = 1.18 (1.12, 1.25)), and mothers of other race/ethnicities (cOR (95%CI) = 1.53 (1.45, 1.62))

also had increased odds of preterm birth compared to non-Hispanic whites. Female infants were less likely than male infants to be born preterm.

Odds of preterm birth increased 2-3% per interquartile increase with entire pregnancy, first trimester and last month of pregnancy seasonalized LUR exposures, in adjusted conditional logistic regression models (Table 4-4). Additionally, preterm birth odds increased approximately 5% per interquartile increase for unseasonalized LUR estimates of NO, NO_2 and NO_x, and approximately 3-5% per interquartile increase for monitored entire pregnancy average BTEX in adjusted models. Effect estimates and confidence intervals were very similar for crude models for all pollutants evaluated (not shown). Average PAHs in the 2nd trimester and vanadium in all pregnancy periods were negatively associated with preterm birth in single pollutant models, although these associations were not robust in two-pollutant models, with null or positive associations, particularly when we adjusted for seasonalized LUR measures (Supplement Figure 4-3). We did not observe associations with any other air toxics, except a weak positive association with benzene exposures in the last month of pregnancy.

In adjusted regression models restricting to women living within 5 miles of the North Long Beach station, LUR exposures were associated with increased odds of preterm birth for unseasonalized as well as seasonalized estimates for the first trimester and entire pregnancy. Entire pregnancy PAH and benzene exposures were associated with approximately 6-9% increased odds of preterm birth per interquartile range increase in pollutant concentration (Table 4-5); weaker positive associations were also observed with last pregnancy month average exposures (not shown). Vanadium exposure was not associated with preterm birth in these analyses.

When stratifying by maternal race, odds of preterm birth for African American mothers were higher than the odds for non-Hispanic whites and Hispanic mothers, for IQR increases in last pregnancy month exposures for LUR-estimated NO, NO_2, and NO_x, and all air toxics (PAHs, BTEX) except for vanadium. (Supplement Table 4-6). Confidence intervals overlapped for most pollutants, but particularly large differences were seen for the seasonalized LUR measures and BTEX across race/ethnicity groups.

Effect estimates for all LUR measures were robust in two-pollutant models, with few differences in point estimates and confidence intervals. Benzene, which had positive associations with preterm birth for entire pregnancy and last pregnancy month estimates in single pollutant models, was less robust in two-pollutant models, with negative effect estimates in some models. Multi-pollutant results are shown graphically in Supplement Figure 4-3.

Air Pollution and Very Preterm Birth

The subset of very preterm births included 3,463 cases and 34,630 matched controls. Mean gestational age was 201.9 days (SD=19.3 days) for very preterm cases. Demographic characteristics were similar to the overall dataset, with some notable exceptions (Table 4-3). Mothers with ≤8 years of education had lower odds of very preterm birth, but higher odds of preterm birth compared to mothers who had completed 12 years of education. The estimated increases in odds of very preterm birth were greater than for preterm birth, for all race groups versus non-Hispanic whites, for mothers receiving no or late prenatal care, and for mothers using government-based insurance or who had no insurance for prenatal care.

LUR-estimated NO, NO_2, and NO_x were associated with approximately 6-10% increased odds of very preterm birth for unseasonalized metrics, as well as seasonalized metrics for 1st trimester, 2nd trimester, entire pregnancy, and last month of pregnancy averages (Table 4-4). Benzene was associated with approximately 20% increased risk of very preterm birth per interquartile increase for entire pregnancy exposures (aOR=1.21, 95% CI=1.15, 1.27). Results for the other BTEX pollutants were similar in size to benzene results (not shown). Positive associations for benzene were also observed for 1st trimester, 2nd trimester, and last pregnancy month averages. Odds of very preterm birth also increased with PAH exposures in the last month of pregnancy, with 8% increased odds per IQR for BAP (95% CI = 1.04, 1.11) and 11% increased odds per IQR for BGP (95% CI 1.06, 1.14).

Similar to the preterm birth results, average PAH exposures in the second trimester and vanadium in all pregnancy periods were negatively associated with very preterm birth risk in single pollutant models. However, in several two-pollutant models (Supplement Figure 4-4), vanadium showed null or positive associations with very preterm birth when controlling for seasonalized LUR measures, as well as PAHs and BTEX pollutants. Similarly, negative associations observed for second trimester BAP exposures also turned positive or null in some two-pollutant models.

Contrary to this, the positive associations observed for single-pollutant LUR and BAP exposures changed minimally in two-pollutant models. Positive associations for benzene were robust for the first trimester and last pregnancy month in two-pollutant models, but somewhat less robust for the entire pregnancy and second trimester estimates.

DISCUSSION

Our results provide new evidence that both measured and modeled traffic exhaust exposures are consistently associated with preterm birth and very preterm birth risk. We demonstrate the utility of seasonally-adjusted LUR modeled exposure estimates that capture both spatial and temporal differences in air pollution, and air toxics measures that could be the causative agents for preterm birth. Our large dataset spanning 12 years of birth data from 4 distinct areas of Los Angeles County allowed us to investigate effect estimates of air toxics using purely temporal comparisons at a single station, to compare effect estimates across race/ethnicity groups, and to evaluate air pollution effects on very preterm birth. Despite low to moderate correlations across unseasonalized LUR, seasonalized LUR and air toxics (PAHs and BTEX) exposure estimates, all three types of measures were associated with increased risk of very preterm birth, suggesting both local exposures (represented by LUR metrics) and also regional exposures (represented by the air toxics measures) contribute to this pregnancy outcome. Preterm birth risk was associated with unseasonalized LUR, seasonalized LUR measures and benzene exposures (entire pregnancy and last month averages), again highlighting the importance of both local and regional air pollution exposures. The entire pregnancy and last pregnancy month periods appeared to be critical windows for benzene and seasonalized LUR measures for both outcomes, and for PAHs and very preterm birth; first and second trimesters benzene and seasonalized LUR exposures were also important for very preterm birth. African American mothers who were highly exposed to traffic-related air pollution

in the last pregnancy month had higher risks of preterm birth compared to White and Hispanic mothers in LA County.

The air toxics analyses restricting to women living within 5 miles of the North Long Beach monitoring station compares subjects based only on seasonal fluctuations and long-term temporal trends, rather than differences in exposure based on spatial distributions. We observe increased odds of preterm birth with PAHs and BTEX exposures among women living within 5 miles (8 km) of the North Long Beach station only. The stronger associations in air toxics observed at this station may be due in part to the higher proportion of African American mothers living near this station (15.0% near North Long Beach versus ~3% near the other stations), who may be more susceptible to these pollutants.[34] The North Long Beach area could also have a more toxic pollutant mix from industrial activities, as this station is located approximately 7 miles (11 km) north of the Ports of Long Beach and Los Angeles, within 0.3 miles (0.5km) of a major freeway (a major diesel truck route), and within 2 miles (3 km) of a small commercial airport. The seasonalized and unseasonalized LUR exposure estimates were also associated with increased preterm birth odds. We observed smaller effect estimates for the unseasonalized LUR versus seasonalized LUR, most likely because the unseasonalized metric relies solely on spatial comparisons, and the range of exposures within this one 5 mile radius may be limited. However, the seasonalized LUR metric incorporates information about both spatial and seasonal differences in air pollution, resulting in greater exposure contrasts.

There were several key differences between the current study and our previous LUR and air toxics study. While there is some overlap, the studies covered different time

periods and geographical areas within LA County, and had different measurement frequencies for the air toxics (every 3 days for MATES, compared to every 12 days for CARB), resulting in differences in the distributions of pollutant exposures (e.g. ranges and means). However, both studies found increased preterm birth odds with benzene and unseasonalized LUR in single-pollutant models, and entire pregnancy seasonalized LUR measures in multi-pollutant models. In contrast to the present study, the MATES-based study reported increased odds of preterm birth with entire pregnancy BAP and BGP exposures. While we did not observe an increased risk in our overall dataset, these PAHs were positively associated with preterm birth for women residing near the North Long Beach station. The MATES program measured PAHs at only two stations (downtown LA and West Long Beach), and the positive associations could be driven by strong associations at the West Long Beach station. Because the MATES West Long Beach station is closer to the ports compared to the CARB North Long Beach station, it is possible that a more toxic mix of pollutants attributable to port shipping and diesel trucking activities could be responsible for these differences in our PAH results. Because of the shorter time frame of the MATES-based study resulting in strong correlations across pregnancy periods evaluated, we could not conclusively identify pregnancy periods of greater susceptibility; therefore, we can not compare trimester-specific or last pregnancy month effect estimates to the present study. Additionally, the smaller study size for the MATES-based study did not allow for stratified analyses or analysis of very preterm birth.

Apart from our LA County studies, only four prior studies using LUR methods to estimate air pollution exposures examined preterm birth as an outcome. The only other

North American study was conducted in Vancouver, Canada based on birth registry records and was the only other LUR-based study to examine associations with very preterm birth (defined as <30 weeks completed gestation).[23] This study also provided a comparison with two other monitoring-based exposure assessment methods, including a nearest monitor approach (zipcode within 10km), and an inverse distance weighted (IDW) approach using the 3 closest stations within 50km of the residential zipcode. The authors reported increased risk of very preterm birth with LUR and IDW-estimated entire pregnancy exposures of NO, NO_2, $PM_{2.5}$. No particular critical window of exposure was apparent similar to our results for very preterm birth, but exposures across the pregnancy periods were highly correlated, i.e. the influence of seasonality was minimal. The only pollutant found to be associated with preterm birth (<37 weeks completed gestation) was IDW-estimated $PM_{2.5}$. These results stand in contrast to our results, where both LUR and monitoring station-estimated NO, NO_2, and NO_x exposures were associated with increased risk of preterm birth. This difference may be due, in part, to a more refined location definition for our LUR measures using residential address geocodes rather than zipcodes, and restricting the population to a smaller radius around each monitoring station (5 miles (8 km) versus 10 km).

The other LUR-based studies of preterm birth were based in Europe, and do not consistently identify any particularly sensitive windows of exposure. All three studies reported strong correlations across trimester-specific and entire pregnancy average exposure estimates, thus hindering their ability to identify conclusively any specific periods of greater sensitivity. A smaller Spanish study using LUR models of NO_2 and benzene reported increased risk of preterm birth among women highly exposed to NO_2 in

the second and third trimesters, and those highly exposed to benzene averaged over the entire pregnancy, although benzene exposures were strongly correlated across pregnancy periods (r~0.72-0.91), limiting their ability to identify confidently periods of greater sensitivity to pollution exposure.[24] Two Dutch studies based on separate large birth cohorts also used seasonalized LUR models, with one reporting no association with LUR-estimated NO_2,[26] and the other reporting positive associations for LUR-estimated NO_2, $PM_{2.5}$ and soot in the last pregnancy month and across the entire pregnancy, although 95% CIs spanned the null.[25]

Prior studies of preterm birth have not been consistent in identifying critical windows of exposure for primary traffic exhaust pollutants, but some studies suggest the first trimester and last month of pregnancy as sensitive periods, though many studies observed associations with entire pregnancy average exposures.[5] Our seasonalized LUR results also identify the first trimester and last pregnancy month as the more sensitive windows, along with entire pregnancy averages indicating that longer-term exposures are also important. Additionally, we observe a sensitive period for BTEX pollutants in the last month of pregnancy. Despite many differences in time periods, demographics (i.e. due to inclusion of different monitoring stations within LA County, and using different inclusion radii around monitoring stations), adjustment variables and study design, the current study identified similar critical windows of exposure as previous studies of traffic-related pollution and preterm birth in the LA basin using criteria pollutant data (see Supplement Table 4-7), although there are differences for specific pollutants in some pregnancy periods. In Wilhelm et al. (2005),[35] we reported increased risks of preterm birth with CO increases in the first trimester and the last 6 weeks before birth, compared

to the current study reporting no association for first trimester CO, and approximately 3% increased risk per 0.5 ppm for the last pregnancy month exposures. In Ritz et al. (2007),[3] we observed increased risks of preterm birth among women more highly exposed to CO, NO_2, and $PM_{2.5}$ in the first trimester, as well as entire pregnancy average and last 6 weeks of pregnancy CO exposures. In the current study, we observed positive associations with first trimester NO, NO_x, and (to a smaller extent) $PM_{2.5}$, last month CO, NO, NO_2, NO_x and $PM_{2.5}$, and entire pregnancy average $PM_{2.5}$ only. Our two prior studies were able to cover a broader geographic distribution across LA County because criteria pollutant data are measured at more SCAQMD stations (compared to only 4 stations for air toxics), and use a smaller radius around the monitoring stations to define inclusion. The inclusion of different populations within LA County may explain some of the differences between our criteria pollutant results compared to prior studies. For the present study, the 5 mile (8 km) distance was chosen as a balance between adequate study size and increases in exposure misclassification. We conducted a sensitivity analysis restricting to women who lived within 3 miles (5 km) of an air toxics station, and the effect estimates were similar.

Only a few studies have examined the impact of air toxics on preterm birth or gestational age. A small study in New York City using personal monitoring at one point in time during pregnancy observed reductions in gestational age and increased risk of preterm birth among African Americans, but not Dominicans, who were highly exposed to PAHs.[34] The authors suggested the difference may be due to healthier dietary practices and greater social support among recent Dominican immigrants. While such personal monitoring approaches may accurately characterize a pregnant woman's PAH

exposures for a short period of time, it may not be valid to extrapolate such short-term exposures to pregnancy periods of biological relevance. Our ambient monitoring and LUR modeling approaches better characterize long-term outdoor exposures, but we could be missing some extremely local exposures such as cigarette smoking (active and passive) and occupational exposures. Other studies of PAHs have demonstrated the formation of DNA adducts, which have been linked to reduced fetal growth, but not preterm birth.[16,17] The biological mechanisms underpinning the effects of air pollution on preterm birth are unknown, although several plausible mechanisms for PAHs have been proposed. PAHs inhaled into the lungs may trigger the production of cytotoxic reactive oxygen species (ROS). For example, it has been hypothesized that preterm birth can be triggered by abnormal cytokine production favoring inflammation, yet inflammatory cytokines may be a normal component of the body's preparation for parturition.[36,37] While studies primarily demonstrated this cytokine response in respiratory tissues,[38-40] inflammatory and oxidant stress responses are also expected to occur at extrapulmonary sites. An alternative hypothesis is that air pollution may increase anti-inflammatory cytokines in the lower genital tract, increasing the risk for infection and subsequent inflammation, which could lead to preterm birth.[41]

Benzene has been linked to increased risk of preterm birth in a Spanish population-based study using LUR-estimated benzene,[24] and in a Chinese occupational study which observed decreases in mean gestational age with maternal benzene exposure. In particular, highly exposed women with susceptible CYP1A1 and GSTM1 genotypes, which affect an individual's ability to detoxify benzene, had larger decreases in gestational age.[10] In experimental studies, benzene has been shown to cross the human

placenta[42] and is associated with reduced fetal weight in animal models.[43] While the biological mechanisms are unknown, benzene can form DNA adducts which can alter enzyme formation and lead to cell death,[43] and metabolites of benzene can cause oxidative stress, which negatively impacts fetal blood cell development.[12-15]

One limitation of this study is the temporal adjustment method used to create seasonalized LUR exposure estimates assumes that NO, NO_2 and NO_x levels at locations within 5 miles (8 km) of the monitoring stations vary in parallel across seasons. This assumption has not been validated and it is plausible that some communities may experience greater or smaller changes in pollution. Validation of this method would require many repeated measurements in different seasons in neighborhoods near established monitoring stations, a task that is expensive to implement. There are also some potential limitations related to using birth certificate data. Gestational age reporting on the birth certificates is based on last menstrual period (LMP) estimates, and there are demonstrated errors with both overestimating and underestimating gestational age.[44-46] While we excluded extreme gestational ages likely due to reporting or recording errors, we still expect outcome misclassification to cause some bias in the preterm birth analysis. However, the case definition for very preterm birth likely excludes most of the truly term births with underestimated gestational age who were previously classified as preterm. Therefore, we expect the very preterm birth case group to represent a mixture of very preterm births and preterm births. Additionally, we may be missing some important potential confounders that are not available on birth certificates, such as smoking, marital status, and alcohol use. However, in a study of preterm birth using birth certificate and survey data, we previously reported that additional control for active and passive

smoking, marital status, and alcohol use did not change criteria air pollutant effect estimates appreciably in models already adjusted for variables available on the birth certificate.[3] Therefore, we expect minimal residual confounding in our results due to these potential confounders. Air pollution has also been linked to increased risk of birth defects,[47] spontaneous abortions,[48] and stillbirth.[49,50] Because aborted fetuses do not appear in standard birth certificates, their exclusion likely caused some selection bias in our study; however, the direction of this bias would be negative, and could have contributed to some of the negative associations observed in our study. While prenatal air pollution exposure causing birth defects could lead to preterm delivery, the focus of this study was on other biological pathways leading to preterm birth. Because we excluded births with recorded defects, our effect estimates were likely biased in a negative direction.

The major strength of this study is the use of LUR-modeling techniques to estimate small-scale spatial variations in traffic pollutant exposure, in combination with ambient air toxics and criteria pollutant data that capture temporal variations in pollutants. These exposure data sources allowed us to examine longer-term spatial contrasts and short-term temporal contrasts in air pollution in our station-stratified analyses. While spatial comparisons may be more susceptible to confounding bias by SES-related variables, these same confounders are highly unlikely to bias the temporal comparisons, lending support to the presence of an effect of traffic related pollutants that is not just attributable to residual confounding.

Additionally, by using a large, racially diverse population-based dataset with air pollution contrasts by season and location, we were able to explore differences in effect

estimates by racial groups, as some studies have suggested differences in susceptibility perhaps due to genetic differences or dietary habits.[6,10] With 12 years of birth data and over 3000 cases, we were also able to examine effects on very preterm births, and to identify critical windows of greater susceptibility in station-stratified models that depended solely on temporal variations.

By using the incidence density method of control sampling matching on gestational age, we ensured pregnancy period-specific exposure estimates were averaged over the same lengths of time and gestational ages for case and matched controls. This approach makes the exposure estimates relevant to the outcome studied, and maintains comparability across cases and controls.

This study provides additional evidence that PAHs and BTEX pollutants from traffic and industrial sources increase a mother's risk of delivering a preterm and even more important, a very preterm baby, and further demonstrate the utility of LUR models to estimate air pollution exposure in pregnancy in a population spanning a large geographical region. Future studies should continue to investigate PAHs and BTEX pollutants, and explore possible differences in susceptibility, particularly across race groups in the region.

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Table 4-1. Pollutant distributions and Pearson's correlation coefficients for entire pregnancy averages for dataset used to evaluate preterm birth (<37 weeks completed gestation)

	Pollutant[1]	n	Mean	IQR[2]	SD[3]
LUR U	NO	143030	32.98	11.2	10.51
	NO_2	143030	27.82	5.25	4.56
	NO_x	143030	60.48	15.5	13.75
LUR S	NO	119913	40.08	23.6	19.80
	NO_2	119913	34.29	10.1	7.70
	NO_x	119913	73.91	32.1	25.81
Toxics	BAP	273175	0.12	0.08	0.05
	BGP	273175	0.54	0.37	0.23
	Total PAH	273175	1.16	0.79	0.48
	BENZ	320642	1.17	0.79	0.59
	EBZ	305150	0.38	0.19	0.16
	TOL	309987	3.06	1.69	1.33
	m,p-XYL	306521	1.42	0.89	0.62
	o-XYL	306627	0.49	0.27	0.22
	V	200894	11.94	6.52	5.18
Criteria Pollutants	CO	384719	1.12	0.63	0.46
	NO	358392	42.22	0.03	19.71
	NO_2	358378	34.93	10.4	7.02
	NO_x	358378	77.05	0.04	24.72
	O_3	386912	35.19	10.7	7.35
	PM_{10}	369077	38.29	8.61	5.90
	$PM_{2.5}$	232469	19.79	4.61	2.85

[1] Pollutant values are expressed in the following units: CO ppm; NO, NO_2, NO_x, ppb; PM $\mu g/m^3$, Benzene, Ethyl Benzene, Toluene, m,p-Xylene, o-Xylene, ppbV; BAP10, BGP10, Total PAH, Vanadium, ng/m3

[2] Interquartile range

[3] Standard deviation

		LUR U[4]			LUR S[5]			TOXICS[6]									CRITERIA POLLUTANTS							
	Pollutant[7]	NO	NO_2	NO_x	NO	NO_2	NO_x	BAP	BGP	Total PAH	BENZ	EBZ	TOL	m,p-XYL	o-XYL	V	CO	NO	NO_2	NO_x	O_3	PM_{10}	$PM_{2.5}$
LUR U	**NO**	1.00																					
	NO_2	0.79	1.00																				
	NO_x	0.98	0.83	1.00																			
LUR S	**NO**	0.67	0.55	0.65	1.00																		
	NO_2	0.56	0.65	0.58	0.79	1.00																	
	NO_x	0.65	0.54	0.66	0.98	0.86	1.00																
Toxics	**BAP**	-0.02	-0.06	-0.03	0.53	0.42	0.54	1.00															
	BGP	-0.01	0.02	-0.02	0.60	0.53	0.62	0.92	1.00														
	Total PAH	-0.01	0.00	-0.02	0.59	0.52	0.61	0.95	0.99	1.00													
	BENZ	0.00	0.10	-0.01	0.52	0.66	0.57	0.69	0.88	0.86	1.00												
	EBZ	0.00	0.15	-0.01	0.41	0.53	0.44	0.54	0.73	0.70	0.90	1.00											
	TOL	-0.02	0.18	-0.02	0.37	0.58	0.41	0.55	0.76	0.73	0.90	0.83	1.00										
	m,p-XYL	0.00	0.14	-0.02	0.43	0.63	0.48	0.52	0.66	0.65	0.84	0.82	0.88	1.00									
	o-XYL	-0.01	0.15	-0.02	0.44	0.62	0.48	0.58	0.76	0.74	0.94	0.93	0.91	0.94	1.00								
	V	-0.04	-0.24	-0.04	-0.36	-0.44	-0.36	-0.25	-0.52	-0.45	-0.50	-0.51	-0.52	-0.30	-0.46	1.00							
Criteria Pollutants	**CO**	0.00	0.09	-0.01	0.57	0.61	0.60	0.71	0.86	0.85	0.93	0.84	0.86	0.80	0.89	-0.58	1.00						
	NO	0.03	0.09	0.00	0.69	0.56	0.68	0.67	0.70	0.72	0.63	0.60	0.56	0.61	0.64	-0.51	0.73	1.00					
	NO_2	0.00	0.16	0.00	0.49	0.73	0.56	0.59	0.74	0.72	0.83	0.78	0.82	0.83	0.86	-0.61	0.84	0.64	1.00				
	NO_x	0.02	0.11	0.00	0.66	0.64	0.68	0.68	0.74	0.75	0.72	0.68	0.66	0.71	0.74	-0.56	0.81	0.98	0.79	1.00			
	O_3	-0.03	0.16	-0.01	-0.51	-0.18	-0.49	-0.45	-0.36	-0.39	-0.07	0.02	0.08	-0.03	0.01	0.01	-0.18	-0.54	0.00	-0.43	1.00		
	PM_{10}	-0.02	0.11	0.01	0.33	0.60	0.41	0.45	0.52	0.53	0.54	0.60	0.54	0.68	0.57	-0.10	0.46	0.13	0.62	0.28	0.28	1.00	
	$PM_{2.5}$	0.01	0.16	0.01	0.32	0.59	0.39	0.41	0.42	0.45	0.75	0.57	0.67	0.80	0.79	-0.05	0.72	0.48	0.79	0.59	0.03	0.75	1.00

[4] Unseasonalized LUR estimates.

[5] Seasonalized LUR estimates.

[6] Abbreviations: LUR U = unseasonalized LUR, LUR S = seasonalized LUR, BAP=benzo(a)pyrene, BGP=benz(g,h,i)perylene, Total PAH = total polycyclic aromatic hydrocarbons (includes Benzo(a)pyrene, Benzo(b)fluoranthene, Benzo(g,h,i)perylene, Benzo(k)fluoranthene, Indeno(1,2,3-cd)pyrene), BENZ=benzene, EBZ=ethyl benzene, TOL=toluene, m,p-XYL = m,p-xylene, o-XYL=o-xylene, V=vanadium

[7] Pollutant values are expressed in the following units: CO ppm; NO, NO_2, NO_x, ppb; PM $\mu g/m^3$, Benzene, Ethyl Benzene, Toluene, m,p-Xylene, o-Xylene, ppbV; BAP10, BGP10, Total PAH, Vanadium, ng/m3

Table 4-2. Pearson's correlation coefficients across pregnancy periods for select pollutants

		MEASURED POLLUTANTS			
Pollutant	**Period**	**1st Trimester**	**2nd Trimester**	**Entire pregnancy**	**Last month of pregnancy**
NO[1]	**1st Trimester**	1			
	2nd Trimester	0.11	1		
	Entire pregnancy	0.54	0.82	1	
	Last month of pregnancy	-0.45	0.15	0.17	1
NO_2	**1st Trimester**	1			
	2nd Trimester	0.52	1		
	Entire pregnancy	0.76	0.90	1	
	Last month of pregnancy	0.07	0.43	0.53	1
BAP[2]	**1st Trimester**	1			
	2nd Trimester	-0.05	1		
	Entire pregnancy	0.44	0.70	1	
	Last month of pregnancy	-0.35	-0.24	-0.02	1
Benzene[3]	**1st Trimester**	1			
	2nd Trimester	0.56	1		
	Entire pregnancy	0.79	0.88	1	
	Last month of pregnancy	0.22	0.29	0.53	1
Vanadium	**1st Trimester**	1			
	2nd Trimester	0.66	1		
	Entire pregnancy	0.85	0.92	1	
	Last month of pregnancy	0.38	0.50	0.62	1

Pollutant	**1st Trimester**	**2nd Trimester**	**Entire pregnancy**	**Last month of pregnancy**
LUR S[4]				
NO[5]	1			
	0.13	1		
	0.54	0.81	1	
	-0.40	0.13	0.25	1
LUR S[6]				
NO_2	1			
	0.51	1		
	0.76	0.90	1	
	0.11	0.49	0.59	1

[1] Correlations for measured and LUR-estimated NO_x were similar to correlations for NO, so only NO is shown

[2] BAP = benzo(a)pyrene; Correlations were similar for all PAH measures, so only BAP is shown

[3] Correlations were similar across all BTEX measures, so only benzene is shown

[4] LUR S = seasonalized LUR

[5] Correlations for measured and LUR-estimated NO_x were similar to correlations for NO, so only NO is shown

[6] LUR S = seasonalized LUR

Table 4-3. Demographic Characteristics by Outcome Group and Crude Odds Ratios (95% CI) for Preterm Birth (<37 weeks completed gestation) and Very Preterm Birth (<32 weeks completed gestation)

Parameter	Cohort[1] (N=415,531) n (%) or mean ±SD	Preterm Cases (N=36,428) n (%) or mean ±SD	Preterm Crude OR (95% CI)
Gestational age (days)	275.6 ± 14.7	244.1±16.9	--
Birth weight (g)	3365.4 ± 495.8	2955.8 ± 664.5	--
Infant gender			
Female	203672 (49.0)	16770 (46.0)	0.88 (0.86, 0.90)
Male	211858 (51.0)	19657 (54.0)	1.0
Missing	1 (0.0)	1 (0.0)	
Maternal age (years)			
<20	48378 (11.6)	4978 (13.7)	1.22 (1.18, 1.27)
20-24	104852 (25.2)	8945 (24.6)	1.0
25-29	113575 (27.3)	9001 (24.7)	0.92 (0.89, 0.95)
30-34	90978 (21.9)	7612 (20.9)	0.97 (0.94, 1.01)
≥35	57748 (13.9)	5892 (16.2)	1.21 (1.16, 1.25)
Missing	0 (0.0)	0 (0.0)	
Maternal race/ethnicity			
Hispanic	291201 (70.1)	26299 (72.2)	1.41 (1.37, 1.47)
White, non-Hispanic	54371 (13.1)	3415 (9.4)	1.0
African American	24634 (5.9)	2800 (7.7)	1.80 (1.71, 1.89)
Asian	25409 (6.1)	1928 (5.3)	1.18 (1.12, 1.25)
Other[2]	19164 (4.6)	1917 (5.3)	1.53 (1.45, 1.62)
Missing	752 (0.2)	69 (0.2)	
Maternal education (years)			
≤8	109866 (26.4)	10496 (28.8)	1.10 (1.07, 1.13)
9-11	91571 (22.0)	8661 (23.8)	1.09 (1.06, 1.13)
12	101123 (24.3)	8828 (24.2)	1.0
13-15	59636 (14.4)	4867 (13.4)	0.93 (0.90, 0.96)
≥16	49895 (12.0)	3223 (8.9)	0.73 (0.70, 0.76)
Missing	3440 (0.8)	353 (1.0)	
Parity			
0	157669 (37.9)	12906 (35.4)	0.90 (0.88, 0.92)

[1] Includes 379,103 births during January 1, 1995 to December 31, 2006 to women residing within 5 miles (8 km) of a CARB air toxics monitoring station; excludes preterm births.

[2] Includes Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, Other (specified).

Parameter	Cohort[1] (N=415,531) n (%) or mean ±SD	Preterm Cases (N=36,428) n (%) or mean ±SD	Preterm Crude OR (95% CI)
1 or more	257754 (62.0)	23503 (64.5)	1.0
Missing	108 (0.0)	19 (0.1)	
Prenatal Care			
No prenatal care or started after 1st trimester	55905 (13.5)	6534 (17.9)	1.44 (1.40, 1.48)
Started in first trimester	357859 (86.1)	29629 (81.3)	1.0
Missing	1767 (0.4)	265 (0.7)	
Mother's Birthplace (U.S. vs outside U.S.)			
U.S. Born	148604 (35.8)	12766 (35.0)	1.0
Foreign Born	266054 (64.0)	23575 (64.7)	1.04 (1.01, 1.06)
Missing	873 (0.2)	87 (0.2)	
Mother's Birthplace			
U.S.	148604 (35.8)	12766 (35.0)	1.0
Mexico	158176 (38.1)	13916 (38.2)	1.03 (1.00, 1.05)
Other outside U.S. (includes Puerto Rico)	107878 (26.0)	9659 (26.5)	1.05 (1.02, 1.08)
Missing	873 (0.2)	87 (0.2)	
Primary Payment for Prenatal Care			
Private, HMO, Blue Cross-Blue Shield	151960 (36.6)	11284 (31.0)	1.0
Medicare, Medi-Cal, government, other non-government programs	251532 (60.5)	23802 (65.3)	1.30 (1.27, 1.33)
No prenatal care, Self pay, no charge, medically indigent, other	11734 (2.8)	1303 (3.6)	1.55 (1.46, 1.65)
Missing	305 (0.1)	39 (0.1)	

Table 4-3, continued

Parameter	Cohort[3] (N=415,531) n (%) or mean ±SD	Very Preterm Cases (N=3,463) n (%) or mean ±SD	Very Preterm Crude OR (95% CI)
Gestational age (days)	275 6 ± 14 7	201 9 ± 19 3	--
Birth weight (g)	3365 4 ± 495 8	2376 8 ± 1062 0	--
Infant gender			
Female	203672 (49 0)	1598 (46 1)	0 89 (0 83, 0 96)
Male	211858 (51 0)	1865 (53 9)	1 0
Missing	1 (0 0)		
Maternal age (years)			
<20	48378 (11 6)	551 (15 9)	1 40 (1 25, 1 57)
20-24	104852 (25 2)	838 (24 2)	1 0
25-29	113575 (27 3)	791 (22 8)	0 86 (0 78, 0 95)
30-34	90978 (21 9)	730 (21 1)	0 99 (0 90, 1 10)
≥35	57748 (13 9)	553 (16 0)	1 21 (1 08, 1 36)
Missing	0 (0 0)		
Maternal race/ethnicity			
Hispanic	291201 (70 1)	2519 (72 7)	1 68 (1 49, 1 90)
White, non-Hispanic	54371 (13 1)	267 (7 7)	1 0
African American	24634 (5 9)	355 (10 3)	2 79 (2 38, 3 27)
Asian	25409 (6 1)	158 (4 6)	1 21 (1 00, 1 48)
Other[4]	19164 (4 6)	157 (4 5)	1 62 (1 35, 1 96)
Missing	752 (0 2)	7 (0 2)	
Maternal education (years)			
≤8	109866 (26 4)	962 (27 8)	0 93 (0 84, 1 02)
9-11	91571 (22 0)	892 (25 8)	1 05 (0 95, 1 15)
12	101123 (24 3)	951 (27 5)	1 0
13-15	59636 (14 4)	395 (11 4)	0 71 (0 63, 0 80)
≥16	49895 (12 0)	231 (6 7)	0 51 (0 44, 0 59)
Missing	3440 (0 8)	32 (0 9)	
Parity			
0	157669 (37 9)	1268 (36 6)	0 95 (0 89, 1 02)
1 or more	257754 (62 0)	2188 (63 2)	1 0
Missing	108 (0 0)	7 (0 2)	
Prenatal Care			
No prenatal care or	55905 (13 5)	883 (25 5)	2 25 (2 07, 2 45)

[3] Includes 379,103 births during January 1, 1995 to December 31, 2006 to women residing within 5 miles (8 km) of a CARB air toxics monitoring station, excludes preterm births

[4] Includes Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, Other (specified)

Parameter	Cohort[3] (N=415,531) n (%) or mean ±SD	Very Preterm Cases (N=3,463) n (%) or mean ±SD	Very Preterm Crude OR (95% CI)
started after 1st trimester			
Started in first trimester	357859 (86.1)	2540 (73.4)	1.0
Missing	1767 (0.4)	40 (1.2)	
Mother's Birthplace (U.S. vs outside U.S.)			
U.S. Born	148604 (35.8)	1301 (37.6)	1.0
Foreign Born	266054 (64.0)	2153 (62.2)	0.93 (0.87, 1.00)
Missing	873 (0.2)	9 (0.3)	
Mother's Birthplace			
U.S.	148604 (35.8)	1301 (37.6)	1.0
Mexico	158176 (38.1)	1264 (36.5)	0.91 (0.84, 0.99)
Other outside U.S. (includes Puerto Rico)	107878 (26.0)	889 (25.7)	0.96 (0.87, 1.05)
Missing	873 (0.2)	9 (0.3)	
Primary Payment for Prenatal Care			
Private, HMO, Blue Cross-Blue Shield	151960 (36.6)	903 (26.1)	1.0
Medicare, Medi-Cal, government, other non-government programs	251532 (60.5)	2347 (67.8)	1.57 (1.45, 1.70)
No prenatal care, Self pay, no charge, medically indigent, other	11734 (2.8)	209 (6.0)	3.12 (2.65, 3.68)
Missing	305 (0.1)	4 (0.1)	

Table 4-4. Adjusted Odds Ratios and 95% Confidence Intervals for preterm birth (<37 weeks completed gestation) and very preterm birth (<32 weeks completed gestation) models, for LUR-based and air toxics exposure estimates averaged. These pollutant exposure estimates have been scaled by their respective inter-quartile ranges, based on the case control cohort for preterm birth (<37 weeks). Models are adjusted for maternal age, race, education, and parity.

	Preterm birth		Very Preterm Birth	
Pollutant	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)
UNSEASONALIZED LUR				
LUR U NO	20586, 120040	1.05 (1.03, 1.06)	1824, 10607	1.08 (1.02, 1.14)
LUR U NO_2	20586, 120040	1.05 (1.03, 1.06)	1824, 10607	1.09 (1.03, 1.16)
LUR U NO_x	20586, 120040	1.04 (1.03, 1.06)	1824, 10607	1.07 (1.02, 1.14)
ENTIRE PREGNANCY				
LUR S NO	17480, 85178	1.02 (1.00, 1.04)	1612, 7924	1.08 (1.03, 1.14)
LUR S NO_2	17480, 85178	1.02 (1.00, 1.04)	1612, 7924	1.10 (1.03, 1.18)
LUR S NO_x	17480, 85178	1.02 (1.00, 1.04)	1612, 7924	1.09 (1.03, 1.15)
benzo(a)pyrene[5]	25602, 172115	0.99 (0.97, 1.01)	2620, 17823	1.16 (1.09, 1.23)
benzo(g,h,i)perylene	25602, 172115	1.00 (0.98, 1.02)	2620, 17823	1.18 (1.11, 1.26)
Benzene[6]	29187, 231348	1.03 (1.02, 1.05)	2835, 23118	1.21 (1.15, 1.27)
Vanadium	18843, 93289	0.96 (0.94, 0.98)	1960, 9973	0.89 (0.83, 0.95)
1st TRIMESTER				
LUR S NO	18222, 91694	1.02 (1.00, 1.04)	1670, 8433	1.08 (1.01, 1.15)
LUR S NO_2	18222, 91694	1.02 (1.00, 1.05)	1670, 8433	1.08 (1.01, 1.16)
LUR S NO_x	18222, 91694	1.02 (1.00, 1.04)	1670, 8433	1.08 (1.01, 1.16)
benzo(a)pyrene	27351, 198818	0.99 (0.97, 1.01)	2742, 20076	1.02 (0.97, 1.08)
benzo(g,h,i)perylene	27351, 198818	0.98 (0.97, 1.00)	2742, 20076	1.02 (0.96, 1.09)
Benzene	32330, 285084	1.00 (0.99, 1.02)	3073, 27158	1.10 (1.05, 1.15)
Vanadium	22586, 138254	0.98 (0.96, 0.99)	2243, 13711	0.97 (0.91, 1.03)
2nd TRIMESTER				
LUR S NO	18187, 91357	1.00 (0.98, 1.02)	1651, 8306	1.07 (1.01, 1.15)
LUR S NO_2	18187, 91357	1.00 (0.98, 1.02)	1651, 8306	1.09 (1.01, 1.17)
LUR S NO_x	18187, 91357	1.00 (0.98, 1.02)	1651, 8306	1.08 (1.00, 1.15)
benzo(a)pyrene	27470, 201155	0.96 (0.94, 0.97)	2739, 20057	0.95 (0.90, 1.00)
benzo(g,h,i)perylene	27470, 201155	0.95 (0.94, 0.97)	2739, 20057	0.98 (0.92, 1.04)
Benzene	32293, 286590	0.99 (0.98, 1.00)	3055, 27059	1.04 (1.00, 1.09)
Vanadium	21829, 128643	0.98 (0.96, 1.00)	2197, 12818	0.92 (0.87, 0.98)
LAST MONTH OF PREGNANCY				
LUR S NO	18422, 93710	1.02 (1.00, 1.04)	1682, 8572	1.06 (1.01, 1.12)
LUR S NO_2	18422, 93710	1.03 (1.01, 1.05)	1682, 8572	1.07 (1.00, 1.15)
LUR S NO_x	18422, 93710	1.02 (1.00, 1.04)	1682, 8572	1.06 (1.00, 1.13)
benzo(a)pyrene	27360, 199898	1.00 (0.99, 1.02)	2749, 20176	1.08 (1.04, 1.11)
benzo(g,h,i)perylene	27360, 199898	1.00 (0.99, 1.02)	2749, 20176	1.11 (1.06, 1.16)

[5] Results for benzo(a)pyrene, benzo(g,h,i)perylene, and total PAHs were similar.

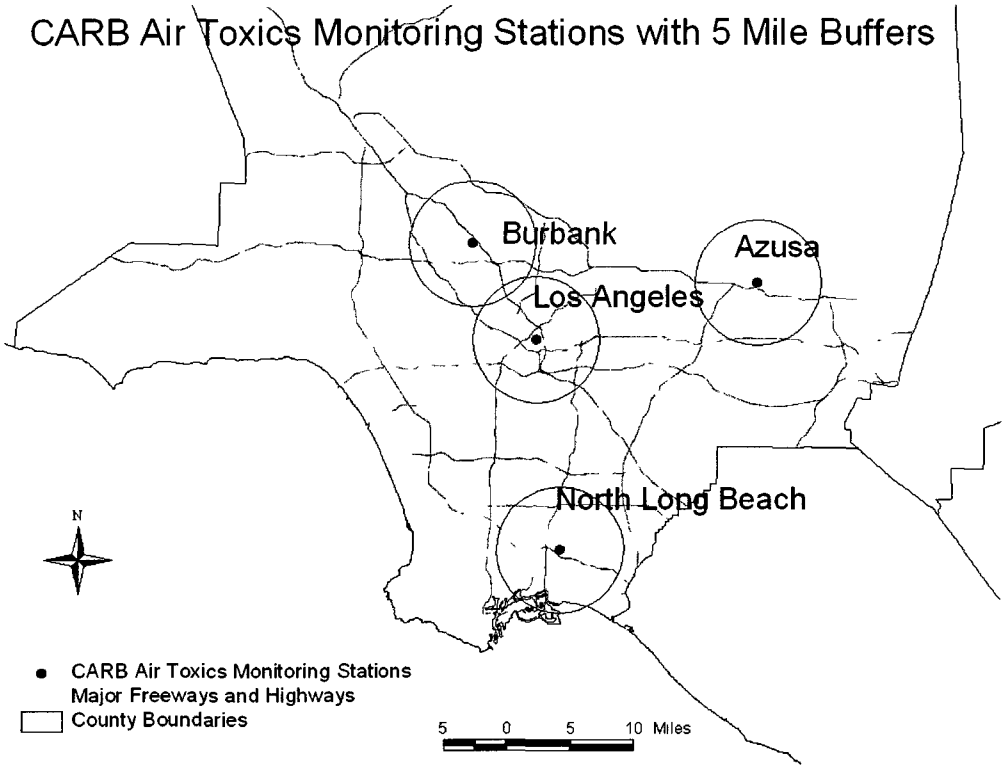
[6] Results for benzene, toluene, ethyl benzene, m,p-xylene, and o-xylene were similar.

Benzene	33368, 304236	1.02 (1.00, 1.03)	3205, 29265	1.10 (1.06, 1.14)
Vanadium	22398, 134518	0.97 (0.95, 0.99)	2287, 13676	0.91 (0.85, 0.97)

Table 4-5. Adjusted Odds Ratios and 95% Confidence Intervals for preterm birth (<37 weeks) models restricted to women residing within 5 miles of the North Long Beach station. Exposure estimates are scaled by the interquartile range for each pollutant. Models are adjusted for maternal age, race, education, and parity.

	North Long Beach	
	N (cases, non-cases)	OR (95% CI)
UNSEASONALIZED LUR		
LUR U NO	4606, 8850	1.02 (0.97, 1.08)
LUR U NO2	4606, 8850	1.03 (0.96, 1.11)
LUR U NOx	4606, 8850	1.03 (0.98, 1.08)
ENTIRE PREGNANCY		
LUR S NO	4588, 8821	1.04 (0.99, 1.10)
LUR S NO2	4588, 8821	1.05 (0.99, 1.12)
LUR S NOx	4588, 8821	1.04 (0.99, 1.10)
benzo(a)pyrene	6198, 13153	1.06 (1.01, 1.11)
benzo(g,h,i)perylene	6198, 13153	1.08 (1.01, 1.14)
Benzene	7256, 17029	1.09 (1.03, 1.15)
Vanadium	4258, 7646	0.98 (0.92, 1.04)

Figure 4-1. CARB air toxics monitoring stations in the Los Angeles Basin



SUPPLEMENTAL MATERIAL FOR CHAPTER 4

Use of ambient air toxics and LUR-modeling approaches to examine preterm birth in Los Angeles County, California

Table 4-6. Supplementary table. Adjusted odds ratios and 95% confidence intervals, stratified by maternal race (African American, Hispanic, non-Hispanic White) for the last month of pregnancy. Adjusted for maternal age, education, parity, and Census-based SES metric. Effect estimates are shown per inter-quartile increase of pollutant exposure.

	African American		Non-Hispanic White		Hispanic	
	OR (95% CI)	n cases, n controls	OR (95% CI)	n cases, n controls	OR (95% CI)	n cases, n controls
SEASONALIZED LUR						
LUR NO	1.19 (1.01, 1.39)	392, 450	1.09 (0.97, 1.21)	826, 1097	1.01 (0.99, 1.03)	13180, 47169
LUR NO_2	1.22 (1.01, 1.47)	392, 450	1.09 (0.96, 1.23)	826, 1097	1.02 (1.00, 1.05)	13180, 47169
LUR NO_x	1.21 (1.02, 1.43)	392, 450	1.09 (0.97, 1.22)	826, 1097	1.01 (0.99, 1.04)	13180, 47169
MEASURED POLLUTANTS						
BAP	1.05 (0.97, 1.13)	814, 990	1.00 (0.96, 1.05)	1423, 2117	1.00 (0.99, 1.02)	19868, 102281
BGP	1.11 (0.99, 1.24)	814, 990	1.00 (0.92, 1.07)	1423, 2117	1.01 (0.99, 1.02)	19868, 102281
total PAH	1.08 (0.98, 1.20)	814, 990	1.00 (0.93, 1.06)	1423, 2117	1.01 (0.99, 1.02)	19868, 102281
Benzene	1.17 (1.06, 1.29)	1107, 1405	0.97 (0.92, 1.04)	2165, 3606	1.01 (1.00, 1.03)	24177, 154724
Ethyl Benzene	1.09 (1.03, 1.16)	1094, 1387	0.98 (0.94, 1.02)	2148, 3570	1.00 (1.00, 1.01)	24043, 152991
m,p-Xylene	1.13 (1.03, 1.23)	1107, 1405	0.96 (0.91, 1.02)	2165, 3606	1.00 (0.99, 1.01)	24176, 154710
o-Xylene	1.15 (1.06, 1.24)	1091, 1388	0.99 (0.94, 1.04)	2159, 3592	1.01 (0.99, 1.02)	23987, 152336
Toluene	1.12 (1.02, 1.23)	1099, 1393	0.99 (0.93, 1.05)	2159, 3593	0.99 (0.98, 1.01)	24060, 153234
Vanadium	0.95 (0.81, 1.12)	572, 666	0.94 (0.84, 1.05)	1072, 1514	0.98 (0.95, 1.00)	16129, 68608
CO	1.12 (1.01, 1.23)	1209, 1534	0.99 (0.93, 1.06)	2541, 4433	1.04 (1.02, 1.05)	25860, 178406
NO	1.16 (1.05, 1.29)	1175, 1489	1.06 (0.99, 1.14)	2437, 4198	1.05 (1.03, 1.07)	25026, 167308
NO_2	1.07 (0.97, 1.17)	1175, 1489	1.02 (0.96, 1.09)	2437, 4198	1.05 (1.04, 1.07)	25027, 167321
NO_x	1.10 (0.99, 1.21)	1175, 1489	1.03 (0.97, 1.11)	2437, 4198	1.06 (1.04, 1.08)	25026, 167308
Ozone	1.01 (0.89, 1.16)	1211, 1536	1.01 (0.94, 1.08)	2546, 4441	0.97 (0.95, 0.99)	25879, 178571
PM_{10}	1.10 (1.00, 1.21)	1219, 1546	1.01 (0.95, 1.07)	2487, 4324	1.00 (0.98, 1.02)	25782, 176983
$PM_{2.5}$	1.04 (0.90, 1.19)	593, 696	1.05 (0.96, 1.14)	1308, 1891	1.01 (0.99, 1.03)	16971, 78004

Table 4-7. Supplementary table. Crude and adjusted odds ratios and 95% confidence intervals for preterm and very preterm birth, for criteria pollutant exposures. Adjusted for maternal age, education, and parity. Effect estimates are shown per inter-quartile increase of pollutant exposure.

	Preterm Birth				Very Preterm Birth			
	Crude		Adjusted[34]		Crude		Adjusted[35]	
Pollutant	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)	N (cases, non-cases)	OR (95% CI)
ENTIRE PREGNANCY								
CO	34846, 334693	0.98 (0.97, 1.00)	34493, 328531	0.99 (0.98, 1.01)	3337, 32201	1.07 (1.02, 1.12)	3302, 31605	1.08 (1.03, 1.13)
NO	32271, 288906	1.01 (1.00, 1.03)	31941, 283534	1.01 (0.99, 1.03)	3075, 27931	1.12 (1.07, 1.18)	3040, 27387	1.13 (1.07, 1.18)
NO_2	32270, 288886	0.97 (0.96, 0.99)	31942, 283554	0.99 (0.98, 1.01)	3074, 27920	1.07 (1.02, 1.13)	3039, 27376	1.09 (1.04, 1.15)
NO_x	32270, 288886	1.00 (0.99, 1.02)	31941, 283534	1.01 (0.99, 1.02)	3074, 27920	1.11 (1.06, 1.16)	3039, 27376	1.12 (1.07, 1.17)
Ozone	35042, 338503	0.99 (0.97, 1.00)	34689, 332292	1.01 (1.00, 1.03)	3352, 32519	0.95 (0.91, 0.99)	3317, 31920	0.97 (0.93, 1.01)
PM_{10}	33869, 311560	0.98 (0.96, 1.00)	33529, 305873	1.00 (0.98, 1.01)	3255, 30303	1.06 (1.00, 1.11)	3221, 29757	1.08 (1.03, 1.14)
$PM_{2.5}$	21293, 123436	1.03 (1.01, 1.06)	21062, 121192	1.05 (1.03, 1.08)	1960, 11429	1.25 (1.15, 1.35)	1935, 11196	1.28 (1.18, 1.39)
1st TRIMESTER								
CO	35767, 351467	0.99 (0.98, 1.01)	35406, 345034	1.00 (0.99, 1.02)	3404, 33446	1.06 (1.02, 1.12)	3368, 32823	1.08 (1.03, 1.13)
NO	34526, 328036	1.03 (1.01, 1.05)	34174, 322002	1.03 (1.01, 1.04)	3262, 30979	1.12 (1.06, 1.18)	3226, 30388	1.13 (1.07, 1.19)
NO_2	34526, 328029	0.97 (0.95, 0.99)	34174, 321995	0.98 (0.97, 1.00)	3262, 30979	1.02 (0.97, 1.07)	3226, 30388	1.04 (0.99, 1.09)
NO_x	34526, 328029	1.02 (1.00, 1.03)	34174, 321995	1.02 (1.00, 1.03)	3262, 30979	1.10 (1.05, 1.16)	3226, 30388	1.11 (1.06, 1.17)
Ozone	35866, 353337	0.96 (0.95, 0.98)	35505, 346883	0.98 (0.96, 0.99)	3410, 33582	0.93 (0.88, 0.98)	3374, 32959	0.94 (0.89, 1.00)
PM_{10}	35462, 343985	0.99 (0.98, 1.00)	35105, 337720	1.00 (0.99, 1.01)	3367, 32674	1.05 (1.01, 1.09)	3330, 32067	1.06 (1.02, 1.11)
$PM_{2.5}$	21925, 132195	1.00 (0.98, 1.02)	21683, 129763	1.01 (0.99, 1.03)	2001, 12058	1.09 (1.02, 1.15)	1975, 11811	1.10 (1.03, 1.17)
2nd TRIMESTER								
CO	35792, 352187	0.96 (0.95, 0.97)	35429, 345753	0.97 (0.95, 0.98)	3389, 33331	1.04 (0.99, 1.09)	3353, 32717	1.05 (1.00, 1.09)
NO	34168, 323296	0.98 (0.96, 0.99)	33815, 317295	0.97 (0.96, 0.99)	3204, 30264	1.05 (1.00, 1.11)	3168, 29685	1.05 (0.99, 1.11)

[34] Adjusted for maternal age, race, education, and parity
[35] Adjusted for maternal age, race, education, and parity

NO_2	34168, 323279	0.97 (0.96, 0.99)	33815, 317278	0.99 (0.97, 1.00)	3204, 30263	1.10 (1.05, 1.16)	3168, 29684	1.11 (1.06, 1.17)
NO_x	34168, 323279	0.97 (0.96, 0.99)	33815, 317278	0.97 (0.96, 0.99)	3204, 30263	1.07 (1.01, 1.12)	3168, 29684	1.07 (1.01, 1.12)
Ozone	35858, 353705	1.03 (1.01, 1.05)	35495, 347248	1.04 (1.02, 1.06)	3395, 33476	0.99 (0.93, 1.05)	3359, 32860	1.01 (0.95, 1.07)
PM_{10}	35447, 344936	0.96 (0.94, 0.97)	35092, 338666	0.96 (0.95, 0.98)	3369, 32751	1.00 (0.96, 1.04)	3335, 32162	1.01 (0.97, 1.05)
$PM_{2.5}$	22624, 140887	0.99 (0.97, 1.00)	22372, 138267	0.99 (0.98, 1.01)	2071, 12843	1.07 (1.00, 1.14)	2046, 12584	1.07 (1.01, 1.14)
LAST MONTH OF PREGNANCY								
CO	36080, 357655	1.03 (1.01, 1.04)	35717, 351128	1.04 (1.02, 1.05)	3430, 34003	1.08 (1.03, 1.12)	3394, 33379	1.08 (1.04, 1.13)
NO	35030, 337630	1.06 (1.04, 1.07)	34675, 331431	1.05 (1.04, 1.07)	3308, 31795	1.08 (1.04, 1.12)	3272, 31195	1.08 (1.04, 1.12)
NO_2	35029, 337607	1.04 (1.02, 1.05)	34674, 331408	1.05 (1.04, 1.07)	3307, 31783	1.14 (1.08, 1.19)	3271, 31183	1.15 (1.10, 1.21)
NO_x	35029, 337607	1.06 (1.05, 1.07)	34674, 331408	1.06 (1.05, 1.08)	3307, 31783	1.10 (1.06, 1.15)	3271, 31183	1.10 (1.06, 1.15)
Ozone	36113, 358071	0.96 (0.94, 0.97)	35750, 351540	0.97 (0.95, 0.99)	3438, 34106	0.96 (0.91, 1.01)	3402, 33480	0.98 (0.93, 1.04)
PM_{10}	35965, 354407	0.99 (0.98, 1.00)	35603, 347931	1.00 (0.99, 1.01)	3413, 33670	1.00 (0.96, 1.04)	3377, 33045	1.01 (0.97, 1.05)
$PM_{2.5}$	23724, 156977	1.00 (0.98, 1.02)	23455, 153953	1.01 (0.99, 1.03)	2149, 14197	1.05 (1.00, 1.11)	2122, 13898	1.06 (1.01, 1.12)

Figure 4-2. Supplementary figure. Directed acyclic graph showing the hypothesized relationships among key variables in the study.

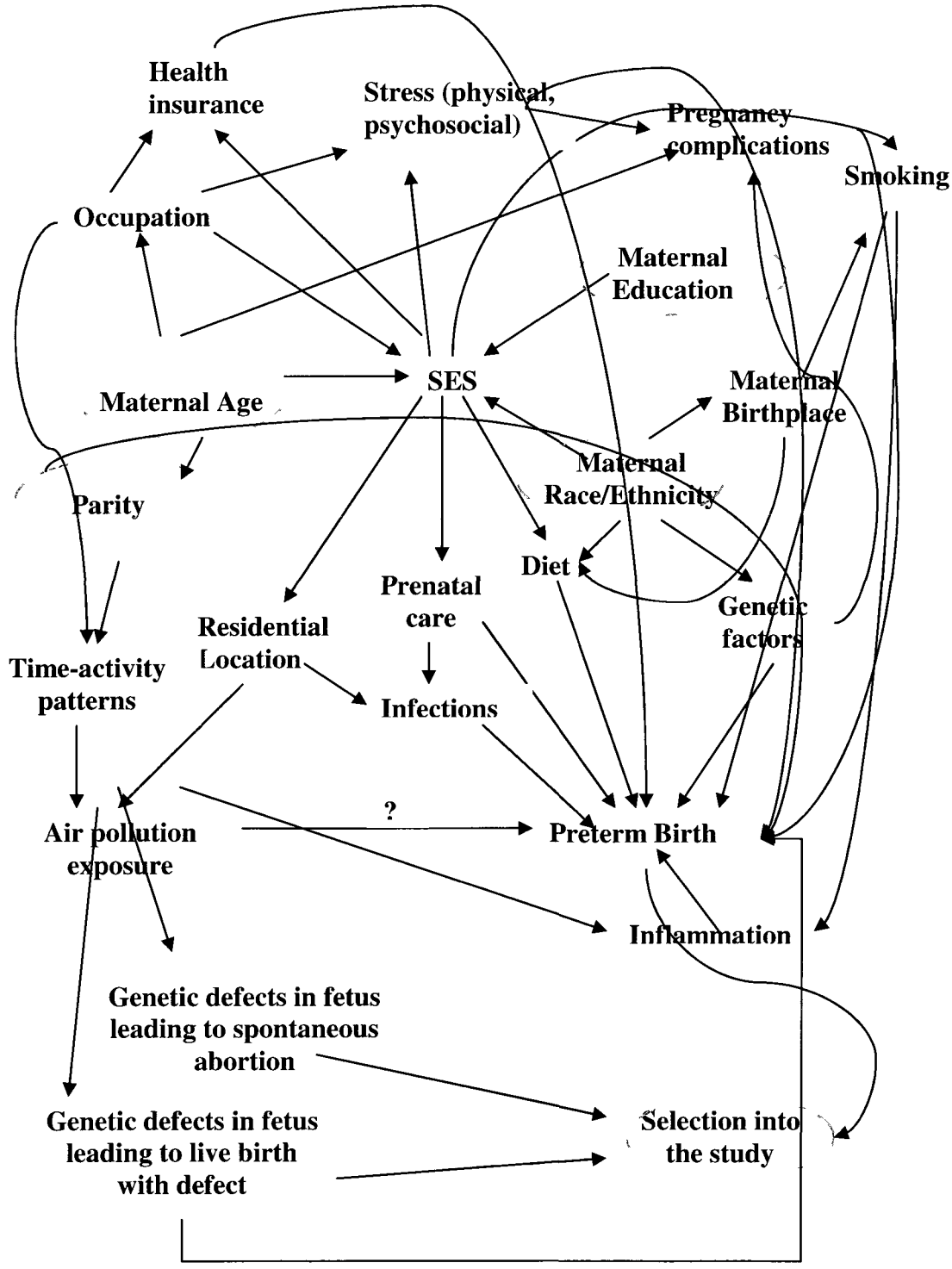
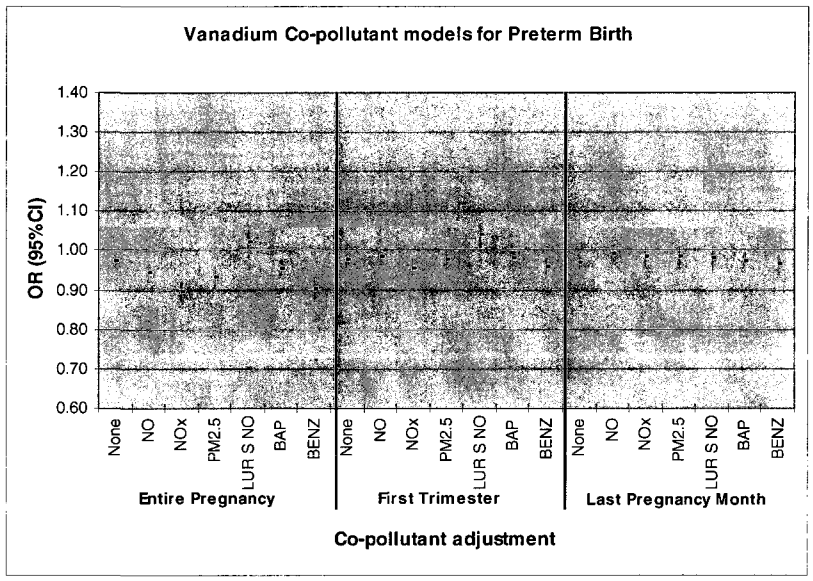
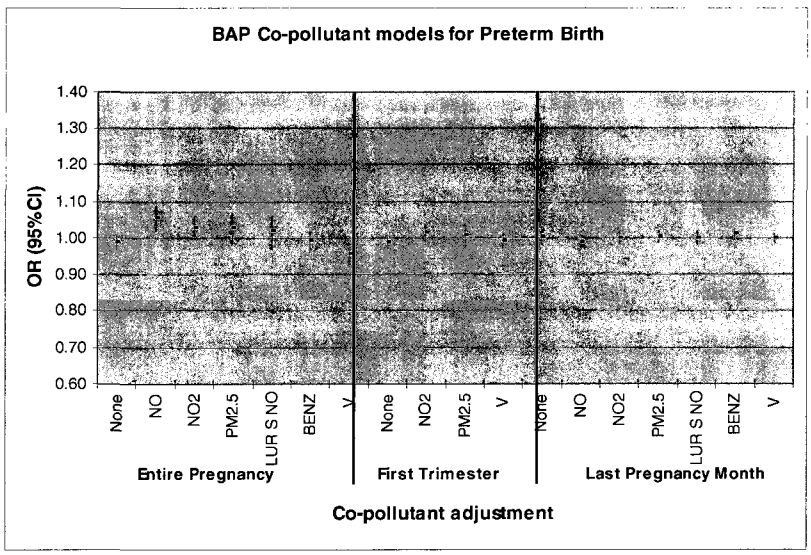
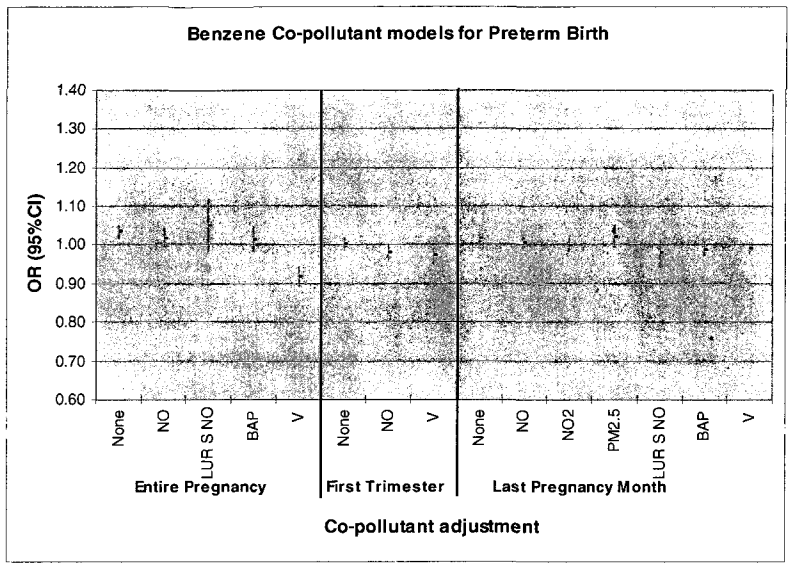
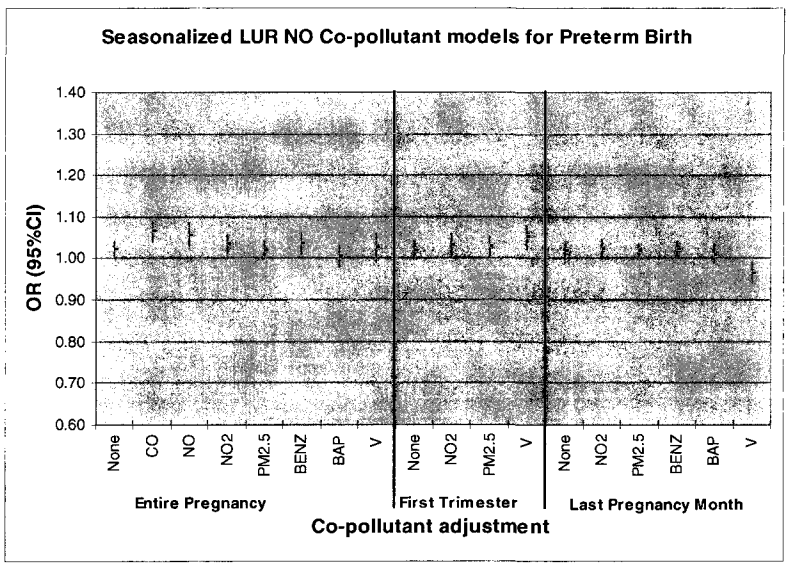


Figure 4-3. Supplementary figure. Two-pollutant model results for Preterm Birth (<37 weeks completed gestation). All models use the exposure estimates scaled by the inter-quartile range for the pollutant period, and are adjusted for maternal age, race/ethnicity, education, and parity. For the Unseasonalized LUR graphs, the pregnancy periods refer to the pregnancy period averages of the co-pollutants only. Results for all LUR-estimated measures were similar, so only NO is shown.






Benzene Co-pollutant models for Preterm Birth
OR (95%CI)
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
None
NO
LUR S NO
BAP
V
None
NO
V
None
NO
NO2
PM2.5
LUR S NO
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment


Seasonalized LUR NO Co-pollutant models for Preterm Birth
OR (95%CI)
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
None
CO
NO
NO2
PM2.5
BENZ
BAP
V
None
NO2
PM2.5
V
None
NO2
PM2.5
BENZ
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment

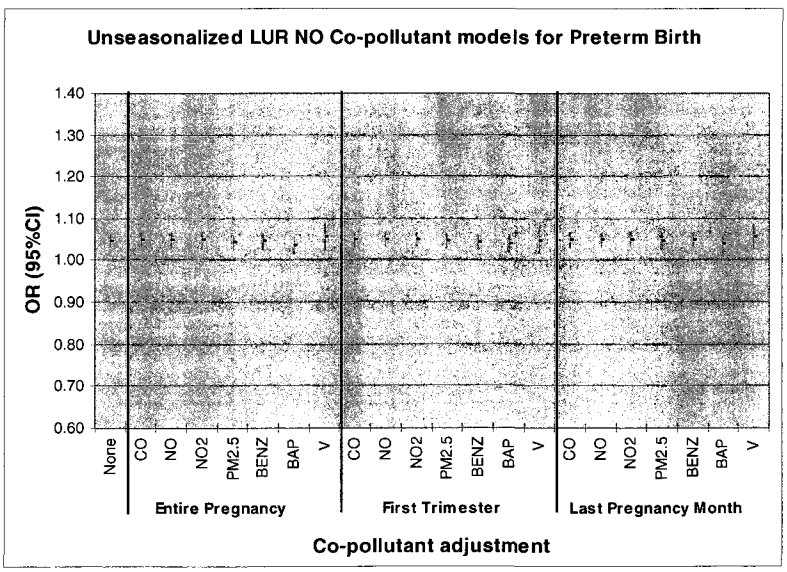
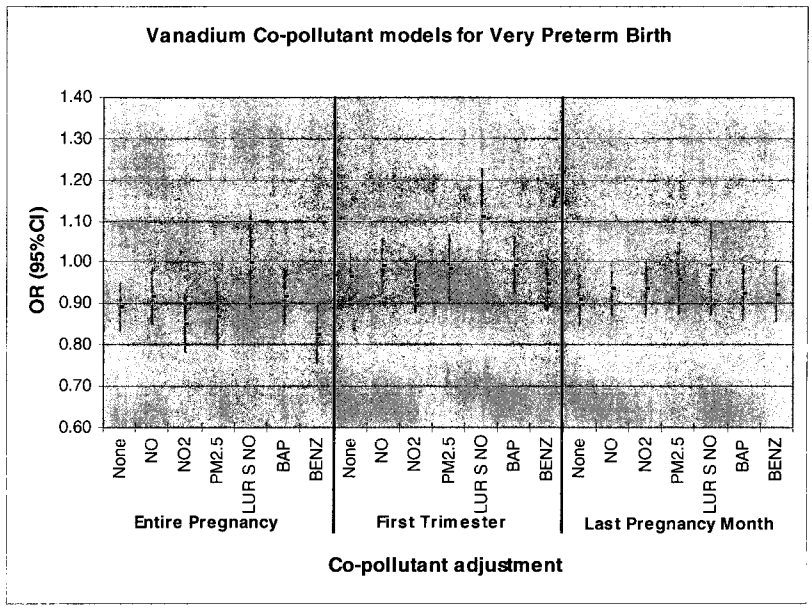
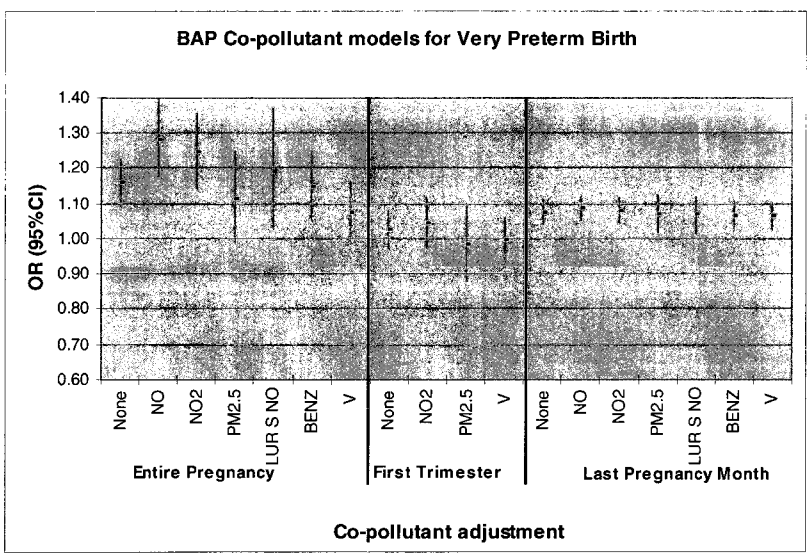
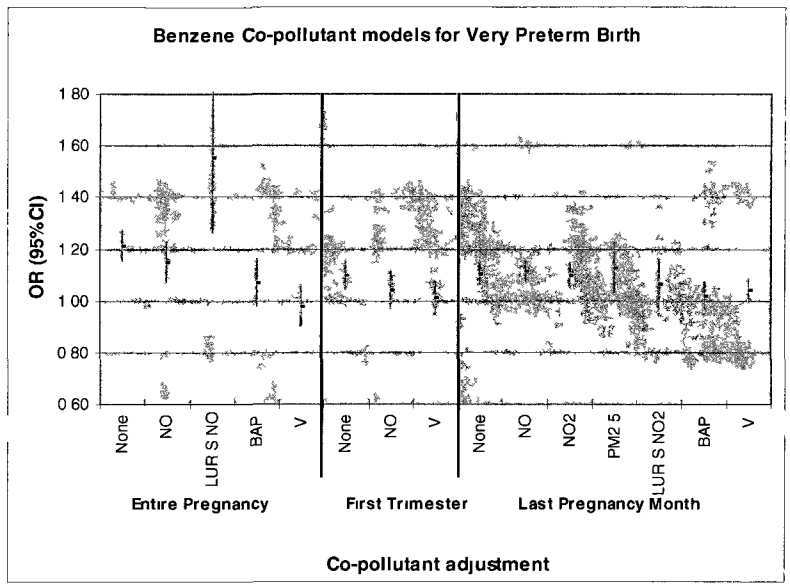
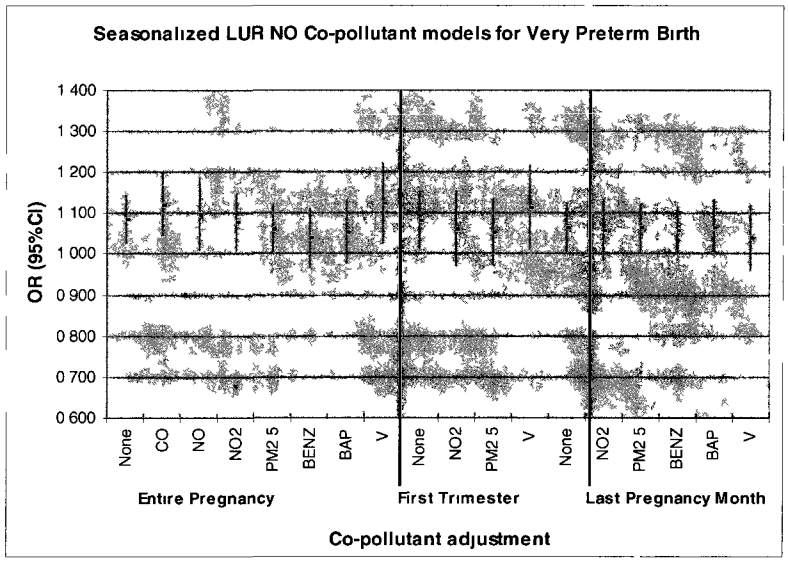

Unseasonalized LUR NO Co-pollutant models for Preterm Birth
OR (95%CI)
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
None
CO
NO
NO2
PM2.5
BENZ
BAP
V
CO
NO
NO2
PM2.5
BENZ
BAP
V
CO
NO
NO2
PM2.5
BENZ
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment

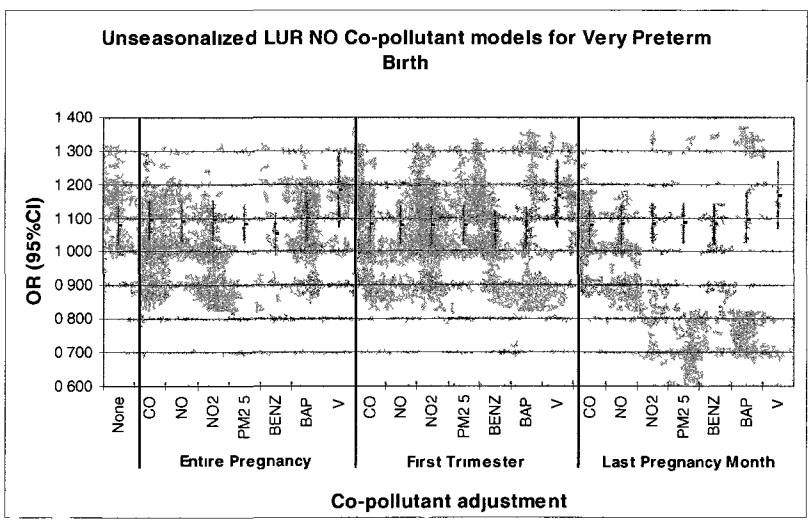
Figure 4-4. Supplementary figure. Two-pollutant model results for Very Preterm Birth (<32 weeks completed gestation). All models use the exposure estimates scaled by the inter-quartile range for the pollutant period, and are adjusted for maternal age, race/ethnicity, education, and parity. For the Unseasonalized LUR graphs, the pregnancy periods refer to the pregnancy period averages of the co-pollutants only. Results for all LUR-estimated measures were similar, so only NO is shown.






Benzene Co-pollutant models for Very Preterm Birth
OR (95%CI)
1 80
1 60
1 40
1 20
1 00
0 80
0 60
None
NO
LUR S NO
BAP
V
None
NO
V
None
NO
NO2
PM2 5
LUR S NO2
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment


Seasonalized LUR NO Co-pollutant models for Very Preterm Birth
OR (95%CI)
1 400
1 300
1 200
1 100
1 000
0 900
0 800
0 700
0 600
None
CO
NO
NO2
PM2 5
BENZ
BAP
V
None
NO2
PM2 5
V
None
NO2
PM2 5
BENZ
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment


Unseasonalized LUR NO Co-pollutant models for Very Preterm Birth
OR (95%CI)
1 400
1 300
1 200
1 100
1 000
0 900
0 800
0 700
0 600
None
CO
NO
NO2
PM2 5
BENZ
BAP
V
CO
NO
NO2
PM2 5
BENZ
BAP
V
CO
NO
NO2
PM2 5
BENZ
BAP
V
Entire Pregnancy
First Trimester
Last Pregnancy Month
Co-pollutant adjustment

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Chapter 5

Survey measures of indoor air quality among recent mothers in Los Angeles County: a study of preterm birth and term LBW

BACKGROUND

While many studies reported on outdoor air pollution and birth outcomes mostly relying on "criteria" air pollutants monitored by government networks for the purpose of compliance with federal regulations, none evaluated indoor air quality even though pregnant women spend on average over 15 hours/day at or near their home, and another 7 hours/day at work or in other indoor locations.[1,2] Indoor air quality may not only be influenced by the intrusion of outdoor pollutants but also by combustion products from tobacco smoke and cooking, and off-gassing of chemical agents from various cosmetic and household products or furniture.[3] Although many studies have reported increased risk of preterm birth and low birth weight with maternal smoking and/or maternal exposure to environmental tobacco smoke (ETS),[4-11] no pregnancy outcome study to date has evaluated the effects of a broader spectrum of agents affecting indoor air quality in high resource countries. The majority of the existing pregnancy outcomes studies of indoor air pollution beyond ETS were conducted in occupational settings,[12-22] or in low or medium resource countries and focused on smoke from biomass fuels.[23-27]

Volatile organic compounds (VOCs) are present in organic solvents used in many cosmetic products (e.g. nail polish or remover, hairspray), cleaners, adhesives, and insecticides for indoor residential use purposes, and may include acetone, 2-butanone, benzene, toluene, xylenes, formaldehyde, and other chemicals.[3,28-30] Most epidemiologic studies of organic solvents have been conducted in occupational settings or examined

only occupational exposures, and have reported increased risks of spontaneous abortion, small for gestational age (SGA), preterm birth, and birth defects, and reductions in birth weight[12-22] Only two studies in high resource countries examined non-occupational indoor air exposures apart from ETS.[31,32] Windham et al.[32] conducted a case-control study of spontaneous abortion in Northern California, and assessed both occupational and non-occupational exposures to organic solvents, although many of the residential-use solvents are unlikely to have been used indoors (e.g. automotive engine cleaners). While women who were occupationally exposed had higher odds of spontaneous abortion, non-occupational use of solvents was not associated with higher odds, except for women who were also occupationally exposed. A recent Danish study investigated prenatal exposure to paint fumes, and reported an inverse association with SGA risk among exposed women, and no increased risk of preterm birth, nor decreases in birth weight.[31] Two other studies examined pregnancy exposure to benzene (mostly through traffic-related pollution rather than specific indoor sources), and reported detrimental effects on fetal growth.[33,34] Residential-use insect sprays once commonly contained organophosphates, although these are gradually being replaced by pyrethroids.[35] Studies have linked prenatal exposure to certain organophosphates to impaired fetal growth and mental development in children.[36-38]

In our study of Los Angeles County mothers, we used survey-based measures of indoor air quality to characterize exposures during distinct pregnancy periods. Here we describe how factors contributing to indoor air quality, including ETS, VOC-containing personal and household product usage, as well as household ventilation influence the risk of preterm birth and term low birth weight (LBW).

METHODS

Subject Selection and Outcome Definition

The UCLA Environment and Pregnancy Outcomes Study (EPOS) was a case-control study nested within the year 2003 birth cohort of all women who resided in 111 zip codes of LA County.[39] The primary goal of EPOS was to study the effects of ambient air pollution on adverse birth outcomes. We used California State and LA County electronic birth certificate records to select live singleton births to mothers residing in zip codes near air pollution monitoring stations and/or major roadways. We included all cases of preterm birth (<37 weeks completed gestation) and LBW (<2,500g) from zip codes (n=27) located near air monitoring stations, and a random sample of 30% of cases from the remainder of the selected zip codes (n=84). Controls (full term, normal weight babies) were matched to cases based on birth month, month that data were received from the county health department, and zip code set, for a total sample of 6,374 women. We reached and enrolled 2,543 of these women (40% response rate) approximately 3-6 months after delivery, including 1,028 cases of preterm birth, 233 cases of term LBW, and 1,282 controls. Compared to non-responders, responders were somewhat more likely to be non-Hispanic white, more educated, nulliparous, and US-born.[39]

Mothers were interviewed in English or Spanish by telephone (58.0%), by mail survey (39.5%), and during home visits (2.6%). Information about maternal age, race/ethnicity, education, birthplace, parity, baby's sex, prenatal care payment source, and complications of pregnancy and delivery was obtained from birth certificates. The EPOS survey questionnaire provided detailed information on other risk factors such as

smoking, alcohol consumption, pet ownership, and household characteristics, including appliance usage and home ventilation. This study was approved by the UCLA Office for the Protection of Human Subjects and the California Committee for the Protection of Human Subjects.

Because cigarette smoking is a major risk factor for both term LBW and preterm birth, and because it is a likely confounder of the relationship between indoor air pollution and these birth outcomes,[11] we restricted our analyses to women who reported never actively smoking (727 preterm cases, 159 term LBW cases, 875 controls, total N=1,761).

Measures of indoor air quality

We evaluated indoor air quality using survey measures of indoor exposures as well as summary measures of indoor air quality to reflect more than one measured exposure contributor and/or home window ventilation that may help mitigate exposures expected to be greater indoors compared to outdoor air.

We assessed the mother's smoking status by asking if she had ever smoked, and then asking how many cigarettes or packs per day during pregnancy, with an option to indicate that she did not smoke during pregnancy. This variable was then categorized as smoked during pregnancy, smoked before but not during pregnancy, never smoked. To assess ETS exposures at home, we also asked about how many people in her household smoked during her pregnancy, and categorized this variable as lived with one or more smokers (home ETS exposed) versus did not live with a smoker (no home ETS). Because household ventilation affects personal exposure to indoor pollutants, we asked

about how often windows were open at home (never, 1 hour/day, half the day, all day, all night, all the time), and further grouped responses as 1 hour/day or never (low/no window ventilation) versus half the day or more (moderate/high window ventilation).

Organic solvent exposure via common personal and household products was assessed by asking about hairspray use, insect spray use, and nail polish use (times per day/week/month or never). We categorized personal and household product usage as never, occasional (using hairspray <10 times/month, using nail polish once/month, using insect spray once/month), regular (using hairspray 10-<30 times/month, using nail polish twice/month, using insect spray >1/month), or frequent use (using hairspray 30 times/month or more, using nail polish more than twice/month).

A summary measure of organic solvent use was created, defining a woman who used one or more of these personal or household products regularly or more frequently as a "Regular/frequent user", while those who used these products with less frequency or who never used these products were considered "Low to Never users". We also examined the combined effects of total organic solvent exposure and window ventilation, categorizing participants as low users and non-users + moderate/high window ventilation, low users and non-users + low/no window ventilation, regular/frequent users + moderate/high window ventilation, and regular/frequent users + low/no window ventilation.

We also created a measure that combined the measures of home ETS exposure and window ventilation, defining the following categories: no home ETS + moderate/high window ventilation, no home ETS + low/no window ventilation, home ETS + moderate/high window ventilation, and home ETS + low/no window ventilation.

Confounding Variables

Based on previous studies,[39,40] the following variables were seen as the key potential confounders to be adjusted for in multivariable analysis: maternal age, race/ethnicity and birthplace, education, and parity (categories and distributions shown in Table 5-1). Other potential confounders included mother's marital status, alcohol use during pregnancy, whether or not the mother lived in a single family home during pregnancy, timing of prenatal care initiation, birth season. Because SES is also an important confounder in our study, we used a variety of measures to characterize SES, including payment source for prenatal care, self-reported family income, whether or not the woman owned or rented the home(s) in which she lived during pregnancy, and a previously-developed metric of socioeconomic status (SES) based on Census block group data, where the block groups were categorized into quintiles based on the SES score.[41,42] Gestational age could be a confounder for the term LBW analysis, and was measured in weeks completed based on birth certificate data.

Statistical methods

We examined the distributions and crude effects of the indoor air quality variables along with demographic and confounding variables in univariate logistic regression models. We used crude and adjusted logistic regression models to examine relations between individual measures of indoor air quality and our birth outcomes of interest (preterm birth and term LBW), restricting to mothers who reported never smoking during pregnancy. Finally, we used crude and adjusted logistic regression models to explore the effects of

the summary measures of indoor air quality, such as the joint effects of ETS exposure and window ventilation.

Adjusted regression models were first adjusted for the key potential confounders (maternal age, race/ethnicity, education, and parity). We then explored additional confounder adjustment, including mother's marital status, birthplace, alcohol use during pregnancy, whether or not the mother lived in a single family home during pregnancy, timing of prenatal care initiation, birth season, the Census-based SES metric, and payment source for prenatal care as a proxy indicator for socioeconomic status (categories shown in Table 5-1). Certain healthy behaviors can also confound our results, so we adjusted for fast food consumption during pregnancy (3-4 days/week or daily/once a week or once a month/never), and prenatal vitamin use (every day or almost every day/yes sometimes/no). We also used multiple imputation software[43] to impute the 16% missing data on family income based on individual and census block group characteristics. For the term LBW analysis, we tried additional adjustment for gestational age (in weeks) and gestational age squared. To account for differences in outdoor air pollution, we also adjusted for entire pregnancy average CO, NO_2, and $PM_{2.5}$, with each pollutant added to the models separately. These pollutant averages were calculated based on ambient monitoring station data from the nearest "best" South Coast Air Quality Management District station, and averaged over the entire pregnancy (for a detailed description, see Ritz et al., 2007).[39]

To examine the potential for exposure misclassification by time spent at home, we stratified the models by whether or not the woman reported working outside the home at

any time during her pregnancy. This stratification was performed in the preterm birth analysis, but not in the analysis of term LBW due to the small number of cases available.

The final models were adjusted for maternal age, education, race/ethnicity, parity and maternal birthplace (US, Mexico, other outside US). Further adjustment for other variables, including imputed income, did not change the main effect estimates by more than 5%.

RESULTS

The large majority of the non-smoking mothers in the study were of Hispanic ethnicity (73.0%), and more than half were having their second or subsequent child (61.1%). Nearly all surveyed women initiated prenatal care in the first trimester (91.2%) and did not use alcohol during pregnancy (94.8%), but 14.3% reported living in a household with one or more smokers. Several indicators suggest that the EPOS population is lower in SES, with over 65% having completed high school or less education, only 35.3% having private insurance for prenatal care, and less than 25% owning any of the homes in which she lived during pregnancy.

More than half the women surveyed reported keeping their windows open at least half the day (57.1%). Some VOC-emitting products were used regularly/frequently, with approximately 15% using hairspray daily or more often and 13.2% using nail polish more than twice a month. However, few women reported using insect spray more than once each month (4.2%). The large majority of women never used any of these VOC-emitting personal and household products.

Table 5-2 shows crude and adjusted associations among never smokers for individual survey measures of personal and household products, ETS and window ventilation. Mothers who used nail polish frequently had slightly increased odds of term LBW. Those who used hairspray occasionally or regularly had small increased odds of preterm birth, although confidence intervals were wide. Other categories of personal product use showed no association with these birth outcomes, with very wide confidence intervals, due to the small number of women who reported using these products. Mothers who lived with one or more smokers had approximately 30% increased odds of term LBW and preterm birth, in adjusted models. Interestingly, women who reported keeping their windows open for half the day or more had approximately 40% decreased odds of term LBW and 20% decreased odds of preterm birth in adjusted models.

Results using the summary measures of indoor air quality are shown in Table 5-3. Among women exposed to ETS at home, those who reported keeping their windows open less than half the day had 3 times the odds of term LBW and 90% increased odds of preterm birth in adjusted models, compared to non-smoking households with frequent window ventilation. Women living with a smoker and reporting frequent window ventilation had no increased risk of either birth outcome. Non-smoking households with infrequent window ventilation also had 40-50% higher odds of term LBW (but not preterm birth), compared to non-smoking households with frequent window ventilation.

None of the women in our study reported regular or frequent use of all 3 personal and household products in our survey. Women who reported regular or frequent use of 1-2 of the specified products had no increased odds of term LBW, and slightly increased odds of preterm birth, although confidence intervals crossed the null (Table 5-3). When

incorporating information about window ventilation, women who had regular/frequent personal and household product usage and low/no window ventilation had very slightly higher odds of term LBW and preterm birth, although confidence intervals mostly overlapped. Women who were regular/frequent users of personal and household products and who kept the windows open at least half the day had no increased risk of either outcome. Because ETS exposure could confound the associations between product use and birth outcomes, we further adjusted these models for home ETS exposure, but effect estimates and confidence intervals changed minimally.

We stratified the preterm birth regression models by whether the woman worked outside the home at any point during her pregnancy and found only a few differences across strata. Compared to never users, regular use of nail polish and hairspray was associated with increased risk of preterm birth among at-home mothers (aOR (95% CI) = 1.72 (1.06, 2.80) for nail polish; 1.71 (0.88, 3.33) for hairspray) but not among working mothers (aOR (95% CI) = 0.80 (0.54, 1.17); 0.73 (0.41, 1.28) for hairspray). Similarly, the summary measure of VOC-emitting product usage and window ventilation showed a positive association among at-home mothers who were regular users of these products who have low window ventilation (aOR (95% CI) = 1.26 (0.89, 1.78)), but not among mothers who worked outside the home (aOR (95% CI) = 0.72 (0.51, 1.02)). Due to the small number of cases, we could not perform this stratification by mother's work status for the term LBW analysis.

Additional adjustment for the outdoor air pollution estimates of CO, NO_2, and $PM_{2.5}$ based on ambient monitoring station data did not appreciably change the associations between any of our indoor air quality metrics for either outcome.

DISCUSSION

Using survey measures of indoor air quality, we found increased risks of term LBW and preterm birth among infants whose mothers reported exposure to ETS and VOC-emitting personal and household products, although increased window ventilation mitigated these risks. To our knowledge, this is one of only three studies to report on residential indoor air quality effects on pregnancy outcomes in a high resource country, beyond studies examining only ETS exposures.[31,32] We were also able to evaluate effect measure modification by home window ventilation, and also adjust for the effects of outdoor air pollution. While exposures to poor indoor air quality in a population-based sample are likely much lower than those for occupational exposures, such studies are important to elucidate exposures potentially affecting all mothers, and not just those who work in specific industries.

The positive associations observed for ETS exposure are not surprising, as epidemiological studies consistently suggest a detrimental effect on birth weight,[6,7,9] although studies of preterm birth are less consistent.[8,10,44] A large California study using cotinine as a marker of ETS exposure reported large increases in preterm birth, fetal death and term LBW risk, and observed a linear dose-dependent relationship with mean birth weight and mean infant length.[5] Our results using the combined metric of ETS exposure and window ventilation further suggest that exposure to ETS at home can be mitigated by improved ventilation. Tobacco smoke is a mixture of gases (CO, PAHs and VOCs) and particles (ultrafine particles (UFP), $PM_{2.5}$).[45] Smoking in confined spaces results in very high pollutant concentrations, but ventilation has been demonstrated to

reduce levels of $PM_{2.5}$ and UFPs.[46,47] While the biological mechanisms are unknown, one review suggested potential pathways for the effects of particulate matter, including systemic oxidative stress, pulmonary and placental inflammation, blood coagulation, endothelial function, and hemodynamic responses affecting oxygen and nutrient transport to the fetus.[48]

The associations observed with VOC-emitting personal and household product usage are weaker than associations observed in occupational studies, as expected. There are few non-occupational studies of such exposures available for comparison. The California study of organic solvent exposure and spontaneous abortion risk included was conducted over 20 years ago, and examined mostly occupational exposures.[32] Non-occupational use of organic solvents was not associated with spontaneous abortion risk, although women who were exposed in both settings had even higher risks compared to those exposed only through work. Comparisons to these studies is not recommended, however, because many of the solvents present in the 1980's (e.g. 1,1,1-trichloroethane) have since been phased out.[49] The recent study of paint fumes at home was based on the Danish National Birth Cohort.[31] Mothers who were exposed to paint fumes during pregnancy (45% of the study population) had a lower risk of SGA; no association was found with preterm birth risk or reduced birth weight. However, this study focused on one very specific source of exposure that occurred over a short period (weeks) during pregnancy. It is possible that the exposure dose over a 1-2 week period is not sufficient to produce a health effect, while more frequent exposures (e.g. daily, several times monthly) may produce a higher overall dose. Pregnant women who were at home during the painting process may have had windows open while the house was being painted and

while the paint was drying, thereby mitigating their exposure to paint fumes. Additionally, cosmetic products that are applied directly to the body (especially hairspray, which is easily inhaled) may result in higher doses of exposure compared to household-level exposures such as paint fumes.

Two other European studies reported effects of benzene on birth weight and fetal growth, but both focused on traffic-related benzene exposures, and neither study investigated potential VOC exposures through personal and household products. A Spanish study that used GIS-modeled ambient exposure estimates and accounted for time-activity patterns in 570 pregnant women reported that exposure to benzene (presumably through traffic exhaust) was associated with decreases in birth weight for exposures averaged over the entire pregnancy, but only for women who spent very little time outdoors in non-residential areas.[33] A prospective study of 271 non-smoking pregnant women in France used personal benzene monitors for a one-week period around the 27th week of gestation.[34] The authors reported that personal benzene exposures were associated with decreased birth weight, head circumference at birth and in the second and third trimester, and decreased biparietal diameter in the first, second and third trimesters. In experimental studies, benzene has been shown to cross the human placenta[50] and is associated with reduced fetal weight in animal models.[51] While the exact biological mechanisms are unknown, benzene can form DNA adducts which can alter enzyme formation and lead to cell death,[51] and metabolites of benzene can cause oxidative stress, which negatively impacts fetal blood cell development.[52-55] While traffic and ETS are the most important sources of benzene exposure among non-smokers on a population level,[56] it is possible that other exposures are important in certain sub-populations, such as

women in occupations that use organic solvents, or who frequently use VOC-containing household and cosmetic products.

Our study has several limitations. As with all retrospective surveys, our results are subject to recall bias, particularly with cases potentially over-reporting and controls under-reporting suspected exposures such as ETS. A French study conducted in 2003-2004 asked recent mothers about pregnancy exposures to ETS in the workplace or through exposure to smoking family members or friends.[57] The authors reported that among non-smoking mothers, over 60% of those who claimed not to be exposed had plasma cotinine levels above the detection limit for ETS used in the study (0.46 ng/ml). However, it is important to note that the prevalence of smoking in France is higher than in California (26% vs. 15%),[58,59] and it is especially low among Hispanic women in California (approximately 7%).[40] Additionally, in California, smoking has been banned in all workplaces (since January 1995) and restaurants and bars (since January 1998),[60] while similar bans in France did not begin until 2007 (public places) and 2008 (restaurants and bars).[61] Therefore, we expect a measure of home ETS exposures to capture the majority of nicotine exposure for most non-smoking women in our population, although it is still possible that cases over-reported ETS exposures to attribute the negative outcome to this cause, and/or cases and controls under-reported such exposures because women did not want to be seen as harming their baby. Reporting of personal and household product usage is also subject to recall bias, but perhaps to a lesser degree than with ETS reporting, because there is less stigma attached to the use of such products.

Although maternal smoking status is often misreported, the predictive value of reported non-smoking is high.[62,63] Therefore, we felt that restricting the dataset to those reported never to have smoked was the best method to account for possible confounding by smoking status in our dataset. However, we also analyzed the effects of indoor air quality in the entire EPOS dataset (n=2,543), and adjusted for maternal smoking. Results were very similar to our original analyses restricting to never smokers, except the effect estimates for the VOC-emitting products moved toward the null for preterm birth. These results are not surprising, as the majority of the women in our dataset reported never having smoked, and the weighted average of all the women in the dataset would mostly reflect the effects among non-smokers. We also expect any biological effect of air pollution on pregnancy smokers to be negligible compared to the effects of smoking during pregnancy, which would pull the overall effect estimates toward the null. Based on previous studies of smoking misclassification, we expect some of the women who reported having quit smoking to be active smokers,[64,65] although few active smokers self-report as non-smokers and most non-smokers accurately report not smoking.[62,63] The low sensitivity of self-reported active smoking results in a downward bias on the effect of smoking on these birth outcomes,[65] and most likely a downward bias on the effects of poor indoor air quality on preterm birth and term LBW if smokers were included in the dataset.

Bias from uncontrolled confounding could be important, particularly in our results for ETS exposure. Lower SES women in our study were more likely to live with a smoker, and SES is also strongly associated with poor birth outcomes.[66] Although we adjusted for several measures of SES, including a Census-based metric, self-reported and

imputed household income, and maternal age, race/ethnicity, and years of education, there could be residual confounding by other SES factors biasing the results upward. Lower SES women are more likely to be exposed to poor air quality both indoors (e.g. ETS exposures) and outdoors, because low SES neighborhoods in Los Angeles County are also areas with higher outdoor air pollution,[67,68] although adjustment for outdoor air pollution using ambient monitoring data did not change our results. Interestingly, women who reported keeping their windows open at least half the day tended to be of a lower-SES profile. Compared to women with less window ventilation, these women were more likely to have lower household incomes, rent their home, use government-based insurance for prenatal care, live in an apartment or condominium rather than a single family home, and somewhat less likely to work outside the home during pregnancy. Additionally, unmeasured healthy behaviors could contribute to a lower risk of term LBW and preterm birth, and could cause residual confounding. For example, women with overall healthy behaviors may keep their windows open more frequently, have lower ETS exposures at home and elsewhere. Our adjustment for maternal birthplace may have partially accounted for confounding by healthy behaviors, since Mexican-born women were far more likely to keep their windows open compared to US-born women (64.7% versus 47.8%), were less likely to live with a smoker (12.2% versus 17.2%), and had somewhat lower risks of delivering a preterm or term low weight baby, compared to US-born mothers. Additional adjustment for maternal birthplace, fast food consumption during pregnancy, and prenatal vitamin use did not change our main results, so we do not believe that these healthful practices are responsible for the observed protective associations between window ventilation and the birth outcomes studied.

There could be other important contributors to indoor air quality that were not included in our study. The EPOS survey also included information about pet ownership, gas appliance usage, carpeting, and attached garages but we did not report these results in the paper. We felt there is a strong likelihood for self selection bias with pet ownership, with women with allergic sensitivities choosing not to have pets. Because few women reported having no gas appliances (heater, stove), the effect estimates were unstable due to the small numbers in the reference category. Carpet and attached garages were not associated with either outcome evaluated. Other potentially important contributors to indoor air quality not evaluated in our survey include cleaning products, household renovation activities including painting, and off-gassing of new carpeting and furniture.

Because we used full-term normal weight babies as the control group for both outcomes, we may have induced an exclusion bias (i.e. a form of selection bias) in our study. Because there is evidence to support an effect of indoor air quality on both preterm birth and term LBW, no single control group provides an unbiased comparison. By excluding preterm babies from the control group for the term LBW cases, we have induced a selection bias. However, if the control group for term LBW cases were defined as all infants born normal weight, including a small number of preterm babies, the effect estimates would likely be biased only slightly downward because of the hypothesized positive association between the exposure and preterm birth. Similarly, defining the control group for preterm cases as all full-term infants, regardless of weight, would have created a likely slight downward bias since the exposure also influenced this outcome but the prevalence of LBW babies among term births is low.

Our study also has several strengths. Using a population-based case-control study design nested within a birth cohort, we were able to evaluate participation bias by comparing participants to non-participants. As previously reported, we compared the distributions of demographic factors reported on birth certificates for survey responders and non-responders, and found that the distributions were similar for the risk factors considered, except there were slightly more non-Hispanic whites, educated mothers, and US-born women among the responders. Regression models showed few differences in effect estimates of ambient air pollution across responder groups, suggesting limited selection bias despite the 40% response rate.[39] Additionally, using survey measures of indoor air quality indicators allowed us to evaluate exposures over the entire pregnancy, rather than using a personal measurement approach which requires extrapolating short-term (e.g. 1-2 week) measures of exposure to represent entire pregnancy exposures. The survey approach also allowed us to evaluate the effects of ventilation, which appears to modify the detrimental effects of ETS and household VOC exposures.

ETS exposures and VOC exposures via personal and household products are associated with risk of preterm birth and term LBW. Fortunately, these adverse associations are mitigated with improved home window ventilation. Pregnant women should be advised to avoid ETS exposure whenever possible, or mitigate ETS exposure by ventilating the home, and take a precautionary approach when using cosmetic products, insecticides, and other household products containing organic solvents.

Table 5-1. Frequencies (percentages) of demographic and indoor air pollution variables among preterm births (N=1,028), term low birth weight (N=233), and control babies (N=1,282) in the EPOS cohort (n=2,543).

	Preterm (N=1,028) n (%)	Control (N=1,282) n (%)	Preterm Crude OR (95% CI)
Birth weight (g) mean ± SD	2809.5 ± 760.6	3415.7 ± 435.7	
Gestational age (days) mean ± SD	241.8 ± 19.4	278.3 ± 10.5	
DEMOGRAPHIC VARIABLES			
Maternal age (years)			
Less than 20	120 (11.7)	120 (9.4)	1.21 (0.89, 1.65)
20-24	222 (21.6)	268 (20.9)	1.0
25-29	240 (23.4)	373 (29.1)	0.78 (0.61, 0.99)
30-34	259 (25.2)	338 (26.4)	0.93 (0.73, 1.18)
35 and older	187 (18.2)	183 (14.3)	1.23 (0.94, 1.62)
Maternal race/ethnicity			
Non-Hispanic White	149 (14.5)	252 (19.7)	1.0
Hispanic White	712 (69.3)	842 (65.7)	1.43 (1.14, 1.79)
Black	87 (8.5)	73 (5.7)	2.02 (1.39, 2.92)
Asian[36]	32 (3.1)	61 (4.8)	0.89 (0.55, 1.42)
Other[37]	43 (4.2)	46 (3.6)	1.58 (1.00, 2.51)
Missing	5 (0.5)	8 (0.6)	
Maternal education			
8 or less years	143 (13.9)	161 (12.6)	0.99 (0.75, 1.30)
9-11 years	225 (21.9)	266 (20.8)	0.94 (0.74, 1.19)
12 years	298 (29.0)	332 (25.9)	1.0
13 to 15 years	163 (15.9)	192 (15.0)	0.95 (0.73, 1.23)
16 more years	185 (18.0)	307 (24.0)	0.67 (0.53, 0.85)
Missing	14 (1.4)	24 (1.9)	
Maternal marital status			
Single, Separated, Divorced, Widowed	216 (21.0)	254 (19.8)	1.20 (0.97, 1.49)
Living together but not married	272 (26.5)	266 (20.8)	1.45 (1.18, 1.77)
Married	534 (52.0)	755 (58.9)	1.0
Missing	6 (0.6)	7 (0.6)	
Payment source for prenatal care			
Private, HMO, Blue Cross-Blue Shield	386 (37.6)	548 (42.8)	1.0
Medicare, Medi-Cal, government, other non-government programs	625 (60.1)	721 (56.2)	1.23 (1.04, 1.46)
No prenatal care, Self pay, no charge, medically indigent, other	16 (1.6)	10 (0.8)	2.27 (1.02, 5.06)
Missing	1 (0.1)	3 (0.2)	
Parity			
1 or more	636 (61.9)	769 (60.0)	1.0

[36] Includes Chinese, Japanese, Korean, Vietnamese, Cambodian, Thai, Laotian, Filipino, Indian, other Asian

[37] Includes Native American, Eskimo, Aleut, Hawaiian, Guamanian, Samoan, Pacific Islanders, and others

	Preterm (N=1,028) n (%)	Control (N=1,282) n (%)	Preterm Crude OR (95% CI)
0	392 (38.1)	513 (40.0)	0.92 (0.78, 1.09)
Maternal birthplace			
Foreign born	610 (59.3)	748 (58.4)	1.05 (0.89, 1.24)
Born in US	416 (40.5)	534 (41.7)	1.0
Missing	2 (0.2)	0 (0.0)	
Maternal birthplace (detailed)			
Mexico	373 (36.3)	500 (39.0)	0.96 (0.80, 1.15)
Other outside US	237 (23.1)	248 (19.3)	1.23 (0.99, 1.53)
US	416 (40.5)	534 (41.7)	1.0
Missing	2 (0.2)	0 (0.0)	
Mother worked outside the home at any point during pregnancy			
No	500 (48.6)	585 (45.6)	1.0
Yes	525 (51.1)	687 (53.6)	0.89 (0.76, 1.05)
Missing	3 (0.3)	10 (0.8)	
Owned the home in which she lived at any point during pregnancy			
Own	260 (25.3)	356 (27.8)	1.0
Rent	757 (73.6)	911 (71.1)	1.14 (0.94, 1.37)
Missing	11 (1.1)	15 (1.2)	
Average monthly rent or mortgage			
<$500	191 (18.6)	196 (15.3)	1.25 (0.95, 1.63)
$500-<750	321 (31.2)	405 (31.6)	1.01 (0.80, 1.28)
$750-<1000	200 (19.5)	264 (20.6)	0.97 (0.75, 1.26)
$1000-<2000	205 (19.9)	262 (20.4)	1.0
$2000+	43 (4.2)	66 (5.2)	0.83 (0.54, 1.27)
Missing	68 (6.6)	89 (6.9)	
Household income			
<$40,000/year	636 (61.9)	746 (58.2)	1.29 (1.05, 1.57)
≥$40,000/year (reference)	224 (21.8)	338 (26.4)	1.0
Missing	168 (16.3)	198 (15.4)	
HEALTH BEHAVIORS			
Prenatal care			
Began in 1st trimester	916 (89.1)	1196 (93.3)	1.0
Began in 2nd-3rd trimester, or no prenatal care	103 (10.0)	79 (6.2)	1.70 (1.25, 2.31)
Missing	9 (0.9)	7 (0.6)	
Smoking status			
Nonsmoker	727 (70.7)	875 (68.3)	1.0
Former smoker	243 (23.6)	349 (27.2)	0.84 (0.69, 1.01)
Pregnancy smoker	57 (5.5)	56 (4.4)	1.23 (0.84, 1.79)
Missing	1 (0.1)	2 (0.2)	
Lived with one or more smokers during pregnancy			
Did not live with smoker	815 (79.3)	1061 (82.8)	1.0
Lived with smoker	206 (20.0)	204 (15.9)	1.32 (1.06, 1.63)
Missing	7 (0.7)	17 (1.3)	
Used alcohol during pregnancy			
No	936 (91.1)	1170 (91.3)	1.0
Yes	90 (8.8)	111 (8.7)	1.01 (0.76, 1.36)

	Preterm (N=1,028) n (%)	Control (N=1,282) n (%)	Preterm Crude OR (95% CI)
Missing	2 (0.2)	1 (0.1)	

Table 5-1, continued

	Term LBW (N=233) n (%)	Control (N=1,282) n (%)	Term LBW Crude OR (95% CI)
Birth weight (g) mean ± SD	2289.9 ± 196.8	3415.7 ± 435.7	
Gestational age (days) mean ± SD	273.7 ± 11.8	278.3 ± 10.5	
DEMOGRAPHIC VARIABLES			
Maternal age (years)			
Less than 20	30 (12.9)	120 (9.4)	1.22 (0.74, 2.00)
20-24	55 (23.6)	268 (20.9)	1.0
25-29	50 (21.5)	373 (29.1)	0.65 (0.43, 0.99)
30-34	59 (25.3)	338 (26.4)	0.85 (0.57, 1.27)
35 and older	39 (16.7)	183 (14.3)	1.04 (0.66, 1.63)
Maternal race/ethnicity			
Non-Hispanic White	31 (13.3)	252 (19.7)	1.0
Hispanic White	154 (66.1)	842 (65.7)	1.49 (0.99, 2.24)
Black	23 (9.9)	73 (5.7)	2.56 (1.41, 4.66)
Asian[38]	12 (5.2)	61 (4.8)	1.60 (0.78, 3.29)
Other[39]	13 (5.6)	46 (3.6)	2.30 (1.12, 4.72)
Missing	0 (0.0)	8 (0.6)	
Maternal education			
8 or less years	37 (15.9)	161 (12.6)	1.59 (1.00, 2.54)
9-11 years	48 (20.6)	266 (20.8)	1.25 (0.81, 1.92)
12 years	48 (20.6)	332 (25.9)	1.0
13 to 15 years	48 (20.6)	192 (15.0)	1.73 (1.12, 2.68)
16 more years	47 (20.2)	307 (24.0)	1.06 (0.69, 1.63)
Missing	5 (2.2)	24 (1.9)	
Maternal marital status			
Single, Separated, Divorced, Widowed	56 (24.0)	254 (19.8)	1.38 (0.97, 1.95)
Living together but not married	55 (23.6)	266 (20.8)	1.29 (0.91, 1.83)
Married	121 (51.9)	755 (58.9)	1.0
Missing	1 (0.4)	7 (0.6)	
Payment source for prenatal care			
Private, HMO, Blue Cross-Blue Shield	87 (37.3)	548 (42.8)	1.0
Medicare, Medi-Cal, government, other non-government programs	143 (61.4)	721 (56.2)	1.25 (0.94, 1.67)
No prenatal care, Self pay, no charge, medically indigent, other	2 (0.9)	10 (0.8)	1.26 (0.27, 5.85)
Missing	1 (0.4)	3 (0.2)	
Parity			

[38] Includes Chinese, Japanese, Korean, Vietnamese, Cambodian, Thai, Laotian, Filipino, Indian, other Asian

[39] Includes Native American, Eskimo, Aleut, Hawaiian, Guamanian, Samoan, Pacific Islanders, and others

	Term LBW (N=233) n (%)	Control (N=1,282) n (%)	Term LBW Crude OR (95% CI)
1 or more	119 (51.1)	769 (60.0)	1.0
0	114 (48.9)	513 (40.0)	1.44 (1.09, 1.90)
Maternal birthplace			
Foreign born	133 (57.1)	748 (58.4)	0.96 (0.72, 1.27)
Born in US	99 (42.5)	534 (41.7)	1.0
Missing	1 (0.4)	0 (0.0)	
Maternal birthplace (detailed)			
Mexico	77 (33.1)	500 (39.0)	0.83 (0.60, 1.15)
Other outside US	56 (24.0)	248 (19.3)	1.22 (0.85, 1.75)
US	99 (42.5)	534 (41.7)	1.0
Missing	1 (0.4)	0 (0.0)	
Mother worked outside the home at any point during pregnancy			
No	101 (43.4)	585 (45.6)	1.0
Yes	130 (55.8)	687 (53.6)	1.10 (0.83, 1.45)
Missing	2 (0.9)	10 (0.8)	
Owned the home in which she lived at any point during pregnancy			
Own	62 (26.6)	356 (27.8)	1.0
Rent	166 (71.2)	911 (71.1)	1.05 (0.76, 1.44)
Missing	5 (2.2)	15 (1.2)	
Average monthly rent or mortgage			
<$500	39 (16.7)	196 (15.3)	1.11 (0.70, 1.76)
$500-<750	71 (30.5)	405 (31.6)	0.98 (0.66, 1.46)
$750-<1000	48 (20.6)	264 (20.6)	1.01 (0.66, 1.57)
$1000-<2000	47 (20.2)	262 (20.4)	1.0
$2000+	14 (6.0)	66 (5.2)	1.18 (0.61, 2.28)
Missing	14 (6.0)	89 (6.9)	
Household income			
<$40,000/year	133 (57.1)	746 (58.2)	1.12 (0.79, 1.57)
≥$40,000/year (reference)	54 (23.2)	338 (26.4)	1.0
Missing	46 (19.7)	198 (15.4)	
HEALTH BEHAVIORS			
Prenatal care			
Began in 1st trimester	198 (85.0)	1196 (93.3)	1.0
Began in 2nd-3rd trimester, or no prenatal care	32 (13.7)	79 (6.2)	2.45 (1.58, 3.79)
Missing	3 (1.3)	7 (0.6)	
Smoking status			
Nonsmoker	159 (68.2)	875 (68.3)	1.0
Former smoker	58 (24.9)	349 (27.2)	0.92 (0.66, 1.27)
Pregnancy smoker	16 (6.9)	56 (4.4)	1.57 (0.88, 2.81)
Missing	0 (0.0)	2 (0.2)	
Lived with one or more smokers during pregnancy			
Did not live with smoker	177 (76.0)	1061 (82.8)	1.0
Lived with smoker	56 (24.0)	204 (15.9)	1.65 (1.18, 2.30)
Missing	0 (0.0)	17 (1.3)	
Used alcohol during pregnancy			
No	207 (88.8)	1170 (91.3)	1.0

	Term LBW (N=233) n (%)	Control (N=1,282) n (%)	Term LBW Crude OR (95% CI)
Yes	26 (11.2)	111 (8.7)	1.32 (0.84, 2.08)
Missing	0 (0.0)	1 (0.1)	

Table 5-2. Crude and adjusted odds ratios and 95% confidence intervals of individual household indoor air pollution variables among never smokers in the EPOS cohort (n=1761).

	Term LBW Cases	Pre-term Cases	Controls	Term LBW Crude OR (95% CI)	Term LBW Adjusted[1] OR (95% CI)	Preterm Crude OR (95% CI)	Preterm Adjusted[2] OR (95% CI)
PERSONAL AND HOUSEHOLD PRODUCTS							
Nail Polish Use							
Never (reference)	89	394	472	1.0	1.0	1.0	1.0
Occasional	22	116	159	0.73 (0.45, 1.21)	0.76 (0.46, 1.27)	0.87 (0.66, 1.15)	0.89 (0.67, 1.19)
Regular	10	66	68	0.78 (0.39, 1.57)	0.81 (0.39, 1.69)	1.16 (0.81, 1.67)	1.20 (0.82, 1.76)
Frequent	31	88	113	1.46 (0.92, 2.30)	1.44 (0.89, 2.32)	0.93 (0.69, 1.27)	0.90 (0.66, 1.24)
Hairspray Use							
Never (reference)	104	420	525	1.0	1.0	1.0	1.0
Occasional	18	97	104	0.87 (0.51, 1.50)	0.88 (0.50, 1.53)	1.17 (0.86, 1.58)	1.19 (0.87, 1.63)
Regular	8	32	33	1.22 (0.55, 2.73)	1.06 (0.46, 2.45)	1.21 (0.73, 2.00)	1.25 (0.74, 2.09)
Frequent	19	104	139	0.69 (0.41, 1.17)	0.68 (0.39, 1.16)	0.94 (0.70, 1.24)	0.94 (0.70, 1.26)
Insect Spray Use							
Never (reference)	132	578	699	1.0	1.0	1.0	1.0
Occasional	9	30	45	1.06 (0.51, 2.22)	1.31 (0.61, 2.82)	0.81 (0.50, 1.30)	0.85 (0.52, 1.38)
Regular	5	30	39	0.68 (0.26, 1.76)	0.62 (0.23, 1.66)	0.93 (0.57, 1.52)	0.86 (0.52, 1.43)
OTHER INDOOR AIR QUALITY CONTRIBUTORS/ MITIGATORS							
Home ETS exposure[3]							
No (reference)	132	607	755	1.0	1.0	1.0	1.0
Yes	27	115	110	1.40 (0.89, 2.22)	1.31 (0.81, 2.12)	1.30 (0.98, 1.73)	1.27 (0.95, 1.70)
Home window ventilation[4]							
Low/no window	81	315	347	1.0	1.0	1.0	1.0

[1] Adjusted for maternal age, race/ethnicity, education, parity, and mother's birthplace (US, Mexico, other outside US)

[2] Adjusted for maternal age, race/ethnicity, education, parity, and mother's birthplace (US, Mexico, other outside US)

[3] Home ETS exposure defined as living with one or more smokers during pregnancy

[4] Home window ventilation measure is based on how often the mother reported keeping windows open during pregnancy. Low/no window ventilation represents 1 hour/day or never. Moderate/high window ventilation represents half the day, all day, all night, and all the time.

ventilation (reference)							
Moderate/high window ventilation	78	408	520	0.64 (0.46, 0.90)	0.58 (0.41, 0.84)	0.86 (0.71, 1.06)	0.80 (0.65, 0.99)

Table 5-3. Crude and adjusted odds ratios and 95% confidence intervals of summary measures of indoor air pollution variables among never smokers in the EPOS cohort (n=1,761).

	Term LBW cases	Pre-term cases	Controls	Term LBW Crude OR (95% CI)	Term LBW Adjusted[44] OR (95% CI)	Preterm Crude OR (95% CI)	Preterm Adjusted[45] OR (95% CI)
Home ETS and home window ventilation[46]							
No home ETS, moderate/high window ventilation (reference)	67	337	443	1.0	1.0	1.0	1.0
No home ETS, low/no window ventilation	65	266	304	1.41 (0.98, 2.05)	1.52 (1.03, 2.25)	1.15 (0.93, 1.43)	1.23 (0.98, 1.55)
Home ETS, moderate/high window ventilation	11	68	73	1.00 (0.50, 1.97)	0.87 (0.43, 1.75)	1.23 (0.86, 1.75)	1.15 (0.80, 1.67)
Home ETS, low/no window ventilation	16	47	37	2.86 (1.51, 5.42)	3.25 (1.65, 6.42)	1.67 (1.06, 2.63)	1.89 (1.17, 3.04)
VOC-emitting personal and household product usage[47]							
Low users and non-users (reference)	90	392	494	1.0	1.0	1.0	1.0
Regular/frequent users	57	254	295	1.06 (0.74, 1.52)	1.05 (0.72, 1.54)	1.09 (0.88, 1.34)	1.08 (0.86, 1.35)
VOC-emitting personal and household product usage and home window ventilation[48]							
Low users and non-users, moderate/high window ventilation (reference)	47	229	306	1.0	1.0	1.0	1.0
Low users and non-users, low/no window ventilation,	43	160	184	1.52 (0.97, 2.39)	1.73 (1.08, 2.78)	1.16 (0.89, 1.53)	1.26 (0.95, 1.67)
Regular/frequent users,	25	139	177	0.92	0.93	1.05	1.03

[44] Adjusted for maternal age, race/ethnicity, education, parity, and mother's birthplace (US, Mexico, other outside US)

[45] Adjusted for maternal age, race/ethnicity, education, parity, and mother's birthplace (US, Mexico, other outside US)

[46] ETS exposure defined as living with one or more smokers. Frequent window ventilation defined as keeping the windows open in her home at least half the day

[47] Moderate personal product use classified as having used 1-2 of 3 specified products (nail polish, hairspray, insect spray) regularly or frequently during pregnancy.

[48] Moderate personal product use classified as having used 1-2 of 3 specified products (nail polish, hairspray, insect spray) regularly or frequently during pregnancy. Window ventilation defined as keeping the windows open (on average) at least half the day.

	Term LBW cases	Pre-term cases	Controls	Term LBW Crude OR (95% CI)	Term LBW Adjusted[44] OR (95% CI)	Preterm Crude OR (95% CI)	Preterm Adjusted[45] OR (95% CI)
moderate/high window ventilation				(0.55, 1.55)	(0.55, 1.59)	(0.79, 1.39)	(0.78, 1.38)
Regular/frequent users, low/no window ventilation	33	131	128	1.68 (1.03, 2.74)	1.83 (1.08, 3.10)	1.37 (1.02, 1.84)	1.50 (1.09, 2.04)

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Chapter 6
Discussion and Public Health Implications

Discussion

These three studies of ambient and residential indoor air pollution make important contributions to the existing literature that has linked traffic exhaust exposures during pregnancy with low birth weight, preterm birth, and other adverse reproductive outcomes. Our studies use several unique data sources and methods to examine these links, to help shed light on potential causative agents, pregnancy periods of greater sensitivity to effects of air pollution exposure, populations with greater susceptibility to air toxics, and important indoor residential sources of air pollution that could be mitigated with behavioral changes. Our studies support the prevailing hypothesis that one or more components of vehicle exhaust and ETS triggers a biological response leading to growth restriction and preterm birth.

Some of our methodological choices warrant a discussion of strengths and weaknesses, and ideas for improving the quality of future studies. LUR models are becoming a more popular choice in air pollution epidemiology research due to their relative cost efficiency and demonstrated high predictive values. They are particularly good at representing spatial variations in air pollutants, which is important in large population-based studies of health outcomes. As discussed previously, researchers have only recently begun to apply LUR methods to estimate pregnancy exposures to air pollution. One of the most important limitations is the lack of validation on the methods used to seasonalize the LUR estimate in order to represent exposures during specific pregnancy periods. There is no consensus about how far we can extrapolate monitoring

station data to be used in these temporal adjustments, and whether local variations in primary exhaust pollutants (represented by the LUR model) follow the same magnitude of temporal fluctuations from one neighborhood to the next. Another possible method for seasonalization could be to create separate LUR models for each season when physical measurements are taken, and then further adjust these models based on monitoring station data. Because of this lack of validation, it is useful for LUR studies to include comparisons to other exposure estimates (as we have done in our studies using criteria pollutant estimate from the closest monitoring station), to help evaluate similarities and differences across exposure assessment methods, while acknowledging the limitations of each method. Additionally, our survey measures of indoor air quality could benefit from validation studies, particularly studies examining specific toxics found in ETS and cosmetic and household products (e.g. organic solvents).

Another challenge in environmental epidemiology studies is in evaluating correlated exposures. In the case of pregnancy air pollution exposures, we have correlations due to pollutants coming from a common source and also due to predictable seasonal fluctuations in pollutant levels causing correlations in exposure estimates across pregnancy periods. Multipollutant models can help disentangle effects of multiple pollutant exposures, and should be explored further in future studies, especially in studies using both air toxics and criteria air pollutant data. These models are also useful in ascertaining the robustness of the single pollutant associations. Correlations across pregnancy periods are particularly common in studies with shorter time frames, or in studies lacking spatial variations in exposures (i.e. lack of exposure contrasts based on spatial differences). Studies should be careful not to draw conclusions about pregnancy

periods of heightened sensitivity to air pollution when exposures across pregnancy periods are highly correlated. The selection of an appropriate study area based on knowledge of air pollution patterns is critical when designing studies of air pollution and pregnancy outcomes.

Finally, there is a selection bias issue stemming from the use of birth certificate data to identify cases and non-cases. Spontaneous abortions and stillbirths are inherently excluded from these studies because they are not recorded in birth certificates. Because ambient and indoor air pollution exposures could plausibly increase spontaneous abortion and stillbirth risk, this exclusion leads to a healthy control selection bias. Future studies should evaluate the magnitude of this bias, and confirm the hypothesis that the bias is in a downward direction.

Public Health Implications

Population-based studies examining health effects of air pollution illustrate the wide-reaching impacts of environmental exposures. Pregnancy effects of air pollution are particularly important because preterm and low birth weight babies have disadvantages in cognitive development and other health outcomes later in life. While some exposures can largely be mitigated through personal choices, such as smoking and use of products containing organic solvents, large reductions in ambient air pollution can only be achieved through policy changes. Policies that could reduce harmful effects of air pollution exposures on a population level include vehicle emissions controls, improved public transportation, banning chemical substances known to be harmful to human health, promotion of cleaner fuels and alternatives to organic solvents, public smoking

regulations, and smarter design of cities to help keep residential zones a safer distance from high traffic roadways and industrial sources of pollution. Additionally, educational programs for smoking cessation should not only target pregnant mothers and women of childbearing age, but also their partners and family members.