Walter A. Rosenblith New Investigator Award

RESEARCH REPORT

HEALTH EFFECTS INSTITUTE

Number 188
July 2016

Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women

Jun Wu, Olivier Laurent, Lianfa Li, Jianlin Hu, and Michael Kleeman

Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women

Jun Wu, Olivier Laurent, Lianfa Li,
Jianlin Hu, and Michael Kleeman

with a Critique by the HEI Health Review Committee

Research Report 188
Health Effects Institute
Boston, Massachusetts

Trusted Science • Cleaner Air • Better Health

Publishing history: This document was posted at *www.healtheffects.org* in July 2016.

Citation for document:

Wu J, Laurent O, Li L, Hu J, Kleeman M. 2016. Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women. Research Report 188. Boston, MA: Health Effects Institute.

 Miranda Design Studio, Inc. Easthampton, Mass., Compositor. Printed by Recycled Paper Printing, Boston, Mass. Library of Congress Catalog Number for the HEI Report Series: WA 754 R432.

Cover paper: made with at least 55% recycled content, of which at least 30% is post-consumer waste; free of acid and elemental chlorine. Text paper: made with 100% post-consumer waste recycled content; acid free; no chlorine used in processing. The book is printed with soy-based inks and is of permanent archival quality.

CONTENTS

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 330 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 1000 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 188, *Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women*, presents a research project funded by the Health Effects Institute and conducted by Dr. Jun Wu of the University of California–Irvine and her colleagues. This research was funded under HEI's Walter A. Rosenblith New Investigator Award Program, which provides support to promising scientists in the early stages of their careers. The report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigators' Report, prepared by Wu and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Critique, prepared by members of the Health Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Critique reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 188

Air Pollution and Adverse Reproductive Health Outcomes in Pregnant Women

INTRODUCTION

There is growing epidemiologic evidence of associations between maternal exposure to ambient air pollution and adverse birth outcomes, such as preterm birth (PTB). Recently, a few studies have also reported that exposure to ambient air pollution may also increase the risk of some common pregnancy complications, such as preeclampsia and gestational diabetes mellitus (GDM). Research findings, however, have been mixed. These inconsistent results could reflect genuine differences in the study populations, the study locations, the specific pollutants considered, the designs of the study, its methods of analysis, or random variation.

Dr. Jun Wu of the University of California–Irvine, a recipient of HEI's Walter A. Rosenblith New Investigator Award, and colleagues have examined the association between air pollution and adverse birth and pregnancy outcomes in California women. In addition, they examined the effect modification by socioeconomic status (SES) and other factors.

What This Study Adds

- Wu and colleagues conducted a comprehensive nested case–control study of air pollution and adverse birth and pregnancy outcomes using birth certificate data in California from 2001 to 2008.
- The study documented associations between increases in various air pollution exposure metrics and increased risks of preterm birth. The evidence was weaker overall for term low birth weight, and many negative associations were found for preeclampsia and gestational diabetes mellitus. Underreporting, especially in groups with lower socioeconomic status, and poor geocoding were listed as potential explanations, but those issues were not fully explored.
- The very large data set and the extensive exposure assessment were strengths of the study.

APPROACH

A retrospective nested case–control study was conducted using birth certificate data from about 4.4 million birth records in California from 2001 to 2008. Wu and colleagues analyzed data on low birth weight (LBW) at term (infants born between 37 and 43 weeks of gestation and weighing less than 2500 g), PTB (infants born before 37 weeks of gestation), and preeclampsia (including eclampsia) of the mother during the pregnancy. In addition, they obtained data on GDM for the years 2006–2008. In the analyses, all outcomes were included as binary variables.

Maternal residential addresses at the time of delivery were geocoded, and a large suite of air pollution exposure metrics was considered, such as (1) regulatory monitoring data on concentrations of criteria pollutants NO_2, $PM_{2.5}$ (particulate matter ≤ 2.5 µm in aerodynamic diameter), and ozone (O_3) estimated by empirical Bayesian kriging; (2) concentrations of primary and secondary $PM_{2.5}$ and $PM_{0.1}$ components and sources estimated by the University of California–Davis Chemical Transport Model; (3) traffic-related ultrafine particles and concentrations of carbon

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Jun Wu at the University of California–Irvine and colleagues. Research Report 188 contains both the detailed Investigators' Report and a Critique of the study prepared by the Institute's Health Review Committee.

monoxide (CO) and nitrogen oxides (NO_x) estimated by a modified CALINE4 air pollution dispersion model; and (4) proximity to busy roads, road length, and traffic density calculated for different buffer sizes using geographic information system tools. In total, 50 different exposure metrics were available for the analyses. The exposure of primary interest was the mean of the entire pregnancy period for each mother.

For the health analyses, controls were randomly selected from the source population. PTB controls were matched on conception year. Term LBW, preeclampsia, and GDM were analyzed using generalized additive mixed models with inclusion of a random effect per hospital. PTB analyses were conducted using conditional logistic regression, with no adjustment for hospital. The main results—adjusted for race and education as categorical variables and adjusted for maternal age and median household income at the census-block level—were derived from single-pollutant models.

MAIN RESULTS AND INTERPRETATION

In its independent review of the study, the HEI Health Review Committee concluded that Wu and colleagues had conducted a comprehensive nested case–control study of air pollution and adverse birth and pregnancy outcomes. The very large data set and the extensive exposure assessment were strengths of the study.

The study documented associations between increases in various air pollution metrics and increased risks of PTB, whereas the evidence was weaker overall for term LBW; in addition, decreases in many air pollution metrics were associated with an increased risk of preeclampsia and GDM, an unexpected result.

The investigators suggested that underreporting in the registry data, especially in lower-SES groups, might have caused the many negative associations found for preeclampsia and GDM. In addition, poor geocoding was listed as a potential explanation, affecting in particular the results that were based on measures of proximity to busy roads and traffic density in the smallest buffer size (50 m). However, those issues were not fully explored. In general, the Committee thought that the analysis of road traffic indicators in the 50 m buffer was hampered by the lack of contrast and that the results are therefore difficult to interpret.

Some other issues with the analytical approaches should be considered when interpreting the results. Only a subset of controls was used, to reduce computational demands. Hence, some models did not converge, especially in the subgroup analyses.

Most of the results in the report were based on analyses using single-pollutant models, which is a reasonable approach but ignores that people are exposed to complex mixtures of pollutants. The Committee believed that the few two-pollutant models that were run provided important insights: these models showed the strongest association for $PM_{2.5}$ mass, whereas components and source-specific positive associations largely disappeared after adjusting for $PM_{2.5}$ mass. This study adds to the ongoing debate about whether some particle components and sources are of greater public health concern than others.

INVESTIGATORS' REPORT

Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women

Jun Wu,[1] Olivier Laurent,[1] Lianfa Li,[1] Jianlin Hu,[2] and Michael Kleeman[2]

[1] *Program in Public Health, University of California–Irvine;* [2] *Department of Civil and Environmental Engineering, University of California–Davis*

ABSTRACT

INTRODUCTION

A growing body of literature has examined the impact of air pollution exposure on adverse reproductive outcomes. However, the existing evidence does not clearly identify the individual pollutants, multipollutant mixtures, or pollution sources that pose the greatest risk—information critical in setting environmental policy that adequately protects vulnerable populations. Several serious gaps remain in the research on the impact of air pollution on pregnancy outcomes. First is the scarcity of studies that consider spatial and temporal parameters of multiple pollutants, particularly the species in particulate matter (PM*) of different sizes, and the lack of source information on PM. Second, few studies have addressed the impact of air pollution on the development of pregnancy complications. Finally, no studies have investigated the effect modification by both maternal obesity and gestational weight gain.

SPECIFIC AIMS

The main objectives of this study were to identify the sources and components of air pollution mixtures that contribute most to adverse reproductive outcomes and to determine the effect modification by socioeconomic status (SES), race, body mass index (BMI), and gestational weight gain. This study had three specific aims:

1. To determine how exposure to local traffic-related air pollution (including polycyclic aromatic hydrocarbons [PAHs] and nitrogen dioxide [NO_2] in a subset) and to ambient concentrations of primary organic aerosols (POA), secondary organic aerosols (SOA), and trace metals in PM affects the risks of adverse birth and pregnancy outcomes (term [> 37 weeks] low birth weight [LBW], preterm birth [PTB], preeclampsia, and gestational diabetes mellitus [GDM]) in California women.
2. To examine the effect modification in California women by SES, smoking, BMI, gestational weight gain, diabetes (both preexisting and gestational), and hypertension (both preexisting and gestational) for PTB and term LBW. (Gestational weight gain was for term LBW only.)
3. To determine the risk of adverse pregnancy outcomes (PTB, term LBW, preeclampsia, and GDM) in a subset of Southern California women from exposure to PAHs and nitrogen dioxide estimated from spatial or spatiotemporal models.

METHODS

Birth certificate records for all births occurring from January 1, 2001, to December 31, 2008, in California (N = 4,385,997) were obtained from the California Department of Public Health. Maternal addresses of

This Investigators' Report is one part of Health Effects Institute Research Report 188, which also includes a Critique by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Jun Wu, Program in Public Health, 653 East Peltason Dr., University of California–Irvine, CA 92697-3957; e-mail: *junwu@uci.edu*.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83467701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

residence recorded on birth certificates were geocoded to the centroid of tax parcels whenever feasible. We obtained records of 4,370,371 pregnancies after excluding infants who were born to women residing outside California and whose addresses could not be geocoded or who had critical identifying information missing.

We developed comprehensive exposure assessment involving a set of advanced exposure modeling methods. The exposure models included a source-oriented chemical transport model that estimates PM concentrations (at a 4 km × 4 km grid resolution) by source, particle-size distribution, and composition; a line-source roadway dispersion model for local traffic emissions; a spatiotemporal model for NO_2; a spatial model for gas-phase PAHs; an empirical Bayesian kriging model for the interpolation of ambient criteria air pollutants; and traffic index estimates.

We analyzed term LBW, preeclampsia, and GDM using the same statistical method for each of these parameters, or cases. Five controls per case were randomly selected from the source population of potential controls. The resulting case-control data sets were analyzed by logistic regression with random effect per hospital using generalized additive mixed models using the mgcv package in R. The main models were adjusted for race/ethnicity and educational level as categorical variables, and for maternal age and median household income at census block-group level using smoothing splines. For the purpose of analyses by subgroup (i.e., stratified by SES and other maternal factors), 10 controls were selected per case to avoid, as much as possible, convergence problems in small subgroups. For PTB, two controls (infants born at 37 or more gestational weeks) matched on the year of conception were randomly selected from the source population. For each control, we truncated exposure estimates at the gestational age reached by the PTB case to which it had been matched. Conditional logistic regression was employed for the analysis of the association between air pollution and PTB, using the survival package in R. For the purpose of subgroup analyses, controls were matched to cases on both the year of conception and the level of the variable considered for stratification (e.g., same education level or smoking status).

RESULTS

We observed a positive association between total measured $PM_{2.5}$ (particulate matter ≤ 2.5 µm in aerodynamic diameter) and PTB, but not term LBW. Both PTB and term LBW were positively associated with some primary and secondary components of ambient air pollution and with primary PM from traffic emissions and meat cooking. PTB was also positively associated with NO_2, with elemental carbon (EC), and very weakly with PM from wood burning. Exposure to EC during the last trimester of pregnancy was also positively associated with term LBW. Regarding secondary pollutants, ozone (O_3) and SOA were positively associated with both term LBW and PTB. Nitrates and ammonium were positively associated with PTB and with term LBW (but only for exposure during the last trimester of pregnancy for term LBW). Organic carbon (OC) was positively associated with PTB but not with term LBW.

We identified several population subgroups in which the associations between primary pollutants and adverse birth outcomes were stronger. Among mothers with a low educational level or chronic hypertension, the association was strong for both PTB and term LBW. Among women living in poorer neighborhoods, of African American or Hispanic race/ethnicity, or with a higher BMI at the beginning of pregnancy, the stronger associations were clear only for PTB.

Many inverse associations were observed between air pollution indicators and either preeclampsia or GDM. This inverse association might be because of the substantial underreporting problem of preeclampsia and diabetes in birth certificate data, especially the higher rates of underreporting in more socioeconomically deprived populations.

INTRODUCTION

Despite tremendous advances in medicine, adverse pregnancy outcomes continue to be major public health concerns. Approximately 8% of live births are LBW (defined as birth weight less than 2500 g), and approximately 10% are PTB (defined as birth before 37 completed weeks of gestation [World Health Organization et al. 2012]) in the United States (Centers for Disease Control and Prevention 1999, 2002). LBW has been associated with increased risks of chronic diseases in later life such as metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases (Chernausek 2012), as well as wheezing and asthma in childhood (Caudri et al. 2007). PTB, a major cause of infant death and morbidity, has been associated with various long-term effects, including impaired vision, hearing, and cognitive function; decreased motor function; and behavioral disorders (Saigal and Doyle 2008).

Other complications are also prevalent in pregnant women. Preeclampsia is a hypertensive syndrome specific to pregnancy, defined as new hypertension (diastolic blood

pressure of ≥ 90 mm Hg) and substantial proteinuria (≥ 300 mg in 24 h) at or after 20 weeks' gestation (Steegers et al. 2010). Preeclampsia and eclampsia affect 2% to 8% of pregnancies worldwide and are major causes of maternal diseases, disability, and death (World Health Organization 2011). GDM, defined as an intolerance to glucose that is first diagnosed or has its onset during pregnancy, occurs in 1% to 14% of pregnancies, depending on race/ethnicity and diagnostic criteria (Ferrara 2007). This complication has serious consequences for both infant and mother, for example, a predisposition to obesity, metabolic syndrome, and diabetes later in life (Fetita et al. 2006).

A growing body of literature has examined the impact of air pollution exposure on pregnancy outcomes because of the susceptibility of the growing fetus to the toxic effects of pollutants. Earlier review papers suggested that air pollution had effects on fetal development, but the evidence was difficult to synthesize because of heterogeneity in study designs, methods, available data, and exposure assessment methods (Glinianaia et al. 2004; Lacasana et al. 2005; Maisonet et al. 2004; Srám et al. 2005; Stillerman et al. 2008; Woodruff et al. 2009). Despite the remarkable variability of the reported results according to study settings and methodologies, two later meta-analyses on LBW and PTB found a statistically significantly positive association between air pollution and the adverse outcomes (Dadvand et al. 2013b; Stieb et al. 2012). But the existing evidence does not clearly identify the individual pollutants, multipollutant mixtures, or pollution sources that pose the greatest risk. This specific information is critical in formulating environmental policy that adequately protects vulnerable populations. Research on the impact of air pollution on pregnancy outcomes faces several serious gaps:

- Few studies consider spatial and temporal parameters of multiple pollutants, particularly species in PM of different sizes, and most studies lack source information on PM.
- Few studies address the impact of air pollution on the development of pregnancy complications.
- No study has examined how both maternal obesity and gestational weight gain modify the effect of pollutants.

PM varies in composition (e.g., in the amount of elemental carbon, nitrates, transition metals [such as zinc, iron, and nickel], PAHs, and other organic compounds). Some of those components of PM can cause oxidative stress and inflammation (Delfino et al. 2010; Schlesinger et al. 2006). The composition of PM varies greatly between seasons and geographical settings and has therefore been hypothesized to modify the relationship between total PM mass and pregnancy outcomes (Bell et al. 2007). In addition, $PM_{0.1}$ (particulates with aerodynamic diameter ≤ 0.1 μm, known as ultrafine particles [UFPs]) have high pulmonary deposition efficiency and large surface areas that can adsorb large amounts of toxic air pollutants (Li et al. 2003). For this reason, UFPs are probably the size fraction with the most redox-active components and the greatest capacity to induce oxidative stress and inflammatory responses (Araujo et al. 2008; Jeng 2010; Li et al. 2003; Ntziachristos et al. 2007; Xia et al. 2004). However, so far, only a few studies have investigated the associations of PM species and UFPs with LBW (Basu et al. 2014; Bell et al. 2010, 2012; Darrow et al. 2011; Ebisu and Bell 2012) and PTB (Darrow et al. 2009; Wilhelm et al. 2011), probably because of the scarcity of data on particle size distribution and speciation data.

There are also open questions, of direct relevance to policy, on the sources of air pollution most likely to cause the adverse pregnancy outcomes. Several recent publications, including our previous work, have suggested a possible influence of primary emissions from vehicular traffic on pregnancy outcomes (Ritz and Wilhelm 2008; Wu et al. 2009b). The influence of other sources of air pollution (e.g., wood burning and meat cooking, both of which notably generate PAHs and other organic compounds) has also been suggested (Boy et al. 2002; Wilhelm et al. 2012). However, only a few studies assessed simultaneously the relative contributions of different sources of air pollution to the risk of adverse pregnancy outcomes (Bell et al. 2010; Dadvand et al. 2014a; Wilhelm et al. 2011).

Further, the impact of air pollution exposure on the development of pregnancy complications has rarely been studied previously. Air pollution exposure might cause pregnancy complications, which in turn might cause adverse birth outcomes. A few studies, including our own, have examined the risk of preeclampsia or gestational hypertension from ambient air pollution exposures, and the reported results were mixed (see Dadvand et al. 2014a; Lee et al. 2013; Malmqvist et al. 2013; Olsson et al. 2013; Pedersen et al. 2014; Pereira et al. 2013; Rudra et al. 2011; van den Hooven et al. 2009; Vinikoor-Imler et al. 2012; Wu et al. 2009b; Xu et al. 2014). However, a recent meta-analysis showed a statistically significant positive association between ambient air pollution exposure and the risk of preeclampsia (Pedersen et al. 2014). There are even fewer studies on ambient air pollution and GDM (Ferrara 2007; Malmqvist et al. 2013; Pereira et al. 2013; van den Hooven et al. 2009) than there

are for preeclampsia. Clearly, more research is needed to elucidate the possible effects of air pollution on the development of pregnancy complications.

Moreover, the increasing prevalence of being overweight and obesity among women of childbearing age is a growing public health concern in the United States (Siega-Riz et al. 2006). Obesity correlates with sociodemographic factors (Chu et al. 2009). Two review papers have documented clear associations of maternal obesity with fetal risks (e.g., miscarriage, PTB, birth defects) and maternal risks (e.g., preeclampsia, GDM) (Krishnamoorthy et al. 2006; Ramachenderan et al. 2008). In addition to obesity, maternal gestational weight gain may be an independent risk factor for adverse reproductive outcomes (Chen et al. 2009; Kiel et al. 2007; Nohr et al. 2009). However, little is known about the effect modification by both maternal obesity and gestational weight gain on the risk of air pollution on reproductive outcomes.

SPECIFIC AIMS

The main objectives of this study were to identify the sources and components of air pollution mixtures that contribute most to adverse reproductive outcomes (i.e., term LBW, PTB, preeclampsia, and GDM) and to determine the effect modification by SES, race, BMI, and gestational weight gain (for birth weight). We addressed the major gaps in literature by comprehensively assessing exposure with several advanced exposure-modeling methods and by using a large database of birth records with the information on potential effect modifiers. The exposure models included a source-oriented chemical transport model that estimates particulate matter concentrations at a 4 km × 4 km grid resolution by source, size distribution, and composition; a line-source roadway dispersion model; a sophisticated spatiotemporal model for NO_2; and an empirical Bayesian kriging model. There were three specific aims in this study:

1. To determine the risks of adverse pregnancy outcomes (term LBW, PTB, preeclampsia, and GDM) in California women from exposure to air pollutants generated by local traffic and to ambient concentrations of POA, SOA, and trace metals in PM.

2. To examine the effect modification in California women by (1) SES, smoking, BMI, diabetes (both preexisting and gestational), hypertension (both preexisting and gestational) for PTB and term LBW, and (2) gestational weight gain for term LBW only.

3. To determine the risk of adverse pregnancy outcomes (PTB, term LBW, preeclampsia, and GDM) in a subset of Southern California women from exposure to PAHs and NO_2 estimated from spatial or spatiotemporal models.

METHODS

DATA SOURCES FOR EXPOSURE ASSESSMENT

Ambient Monitoring Station Data

We obtained 2000–2008 air quality data for the entire state of California from the routine monitoring network of the U.S. Environmental Protection Agency (EPA) Air Quality System (*www.epa.gov/aqs*). Criteria air pollutants (NO_2, O_3, and $PM_{2.5}$) were extracted. Hourly measurements of gaseous pollutants were converted to daily means and then monthly means using a 75% completeness criterion. Because real-time PM measurements account for < 10% of the total data and there are systematic differences between real-time and filter measurements, we included only filter-based PM measurements that were typically conducted every third or sixth day. Monthly means for PM were calculated if there were three or more daily concentrations per month. Table 1 presents the numbers of the monitoring stations and the summary statistics (median, mean, 5% and 95% percentiles, and interquartile range) for the metrics of air pollutants ($PM_{2.5}$, O_3, and NO_2) after removal of missing values. No imputation was used to fill in the missing values.

Roadway and Traffic Data

We obtained roadway data from the ESRI StreetMap North America 10.0 (ESRI, Redlands, CA, *www.esri.com*). This data set was bundled with ArcGIS software products and included 2005 TeleAtlas street data. We obtained the 2002 annual average daily traffic (AADT) counts from the California Department of Transportation (Caltrans), which provides traffic data on highways and major arterial roads. AADT was produced by Caltrans staff from a combination of measurements and modeled values as an alternative to limited traffic counts.

Hourly total traffic and truck counts (2001–2008) on highways were obtained from the Caltrans Performance Measurement System (PeMS) (*http://pems.dot.ca.gov*). We averaged the total and truck traffic counts at the PeMS monitoring sites and assigned the point PeMS data to adjacent roadway segments (< 300 m) with matching street names, which were then extended to contiguous

Table 1. Brief summary of U.S. Environmental Protection Agency monitoring station data in California, 2000–2008, for three air pollutants

Pollutant	Total number of stations	Number of stations with valid month measurements	Median	Mean	5th percentile	95th percentile	Interquartile range
$PM_{2.5}$ (μg/m^3)	117	75–98	9.4	11.2	2.6	26.1	8.0
O_3 (ppb)	243	151–182	41.1	42.1	18.5	69.7	20.6
NO_2 (ppb)	148	94–109	13.6	15.4	2.9	33.6	11.7

Note: $PM_{2.5}$ = particulate matter ≤ 2.5 μm in aerodynamic diameter; O_3 = ozone; NO_2 = nitrogen dioxide.

road segments (within 15 km) with matching street names. For surface streets or highways that had no PeMS measurements, we scaled 2002 traffic counts using county-specific vehicle miles traveled (*http://traffic-counts.dot.ca.gov*). Thus, our final traffic count data set was a combination of measurement and estimated values.

Land-Use Data

We first obtained the 2001 land-use data from the Southern California Association of Governments (SCAG) (Park and Stenstrom 2008). These data were first developed using 1990 aerial photographs and updated using computer-interactive photointerpretation techniques and digital orthophotography with 1 m resolution. Later, we obtained the 2008 InfoUSA (*https://www.infousa.com*) data for neighborhood businesses from SCAG.

Meteorological Data

Hourly meteorological data for 2000–2008 were obtained from a composite database compiled by the California Air Resources Board (*www.arb.ca.gov/aqmis2/metselect.php*). This data set came from various sources, including data collected by the EPA through its Aerometric Information Retrieval System (AIRS) and data collected by the National Interagency Fire Center through its Remote Automated Weather Stations. Hourly ambient parameters (temperature, °C; relative humidity, %; wind speed, meters per second; wind direction, degree; and precipitation, millimeters) were retrieved. There were 390 to 473 (23–30 for Los Angeles) meteorological monitoring sites for atmospheric temperature, 378 to 450 (20–35 for Los Angeles) for wind speed and direction, 253 to 450 (17–20 for Los Angeles) for precipitation, and 305 to 381 (22–27 for Los Angeles) for relative humidity.

Additionally, we obtained Pasquill atmospheric stability classes every 3 hours at approximately 40 km × 40 km spatial resolution from the National Oceanic and Atmospheric Administration Air Resources Laboratory archive of the Eta 4-D Data Assimilation System (*www.arl.noaa.gov/ready.html*). We assigned an atmospheric stability class from the nearest modeling grid to each sampling site.

Satellite and Other Data

Greenness data were used in the spatiotemporal modeling of NO_2 in Los Angeles as a covariate and in examining the potential benefit of greenness on pregnancy outcomes. We used the normalized difference vegetation index (NDVI) (Tucker 1979) to characterize greenness exposure (Dadvand et al. 2012b; Villeneuve et al. 2012). NDVI is the ratio of the difference between the near-infrared region and red reflectance to the sum of these two measures [i.e., NDVI = (band 4 − band 3) / (band 4 + band 3)], where band 4 and band 3 are the surface reflectance acquired by the near-infrared and red bands, respectively, of Landsat sensors. We obtained a set of mostly cloud-free 30 m × 30 m Landsat scenes from the Global Land Survey 2005 (U.S. Geological Survey) data set covering California. The data consist of orthorectified Landsat 5 and gap-filled Landsat 7 data acquired during the leaf-on season for the location. Scenes of low quality or excessive cloud cover were replaced with scenes acquired in 2004, 2007, or 2008. We processed all the Landsat scenes for atmospheric correction and converted them to surface reflectance with the Landsat Ecosystem Disturbance Adaptive Processing System algorithm (Masek et al. 2012) before calculating the NDVI.

From the Landsat Enhanced Thematic Mapper data, we extracted land-surface temperature using Environment for Visualizing Images software (ITT Visual Information Solutions, Boulder, CO) and converting the thermal bands to land-surface temperature using a formula developed by Yale Center for Earth Observation (YCEO 2010). We also

obtained elevation data at a 10 m × 10 m resolution from the U.S. National Elevation Dataset (*http://nationalmap.gov*). Finally, we obtained block-level population data from the U.S. Census 2000 (U.S. Census Bureau 2000).

EXPOSURE MODELING

Empirical Bayesian Kriging of Criteria Air Pollutants in California

Classical kriging assumes that the single semivariogram is the true semivariogram of the observed data. Thus, the interpolated surface is generated from a Gaussian distribution, with the correlation structure defined by the single estimated semivariogram. This strong assumption may not be applicable in practice for the spatial distribution of air pollutants, because of insufficient representative samples of air pollutants. Thus, for the interpolation of air pollutants, we used empirical Bayesian kriging (EBK), an approach that incorporates the uncertainties introduced by estimating the underlying semivariogram (Gribov and Krivoruchko 2012). Compared with the classical kriging methods, EBK has the following advantages: (1) automatic variogram modeling (minimal manual interaction), thus improving the efficiency; (2) standard-error estimation; (3) more accurate predictions of moderately nonstationary data; and (4) more accurate prediction (less underestimation or overestimation than classical kriging methods) for small data sets (Krivoruchko 2012).

The EBK model uses iterations of semivariogram estimations and the Bayes rule. The main steps of the model (Krivoruchko 2012) are as follows:

1. A semivariogram model is estimated using the monitoring station data.
2. A new value is simulated for each input data location, using the estimated semivariogram.
3. A new semivariogram model is estimated from the simulated data, and a weight for this semivariogram is calculated using the Bayes rule, which indicates the likelihood of the observed data generated by the updated semivariogram.
4. Steps 2 and 3 are repeated a specific number of times, and the prediction with its errors is finally produced at the unsampled locations using these semivariogram models and their corresponding weights.

We used EBK in ArcGIS 10.1 (ESRI, Redlands, CA) to generate monthly surface concentrations of criteria air pollutants (NO_2, $PM_{2.5}$, and O_3) at 200 m × 200 m resolution in California from 1999 to 2008. For standard-error estimation, we simulated 200 semivariograms for each monthly run. Exposure to air pollutants and the standard error of estimation were extracted from the monthly surface concentrations to each maternal residence and then averaged over specific pregnancy periods (the first, second, and third trimesters and the entire pregnancy). We also conducted leave-one-out cross-validation for the EBK estimates of the three air pollutants. The results seemed reasonable for the monthly means: NO_2 (R^2 = 0.74; root mean square error [RMSE]: 6.08 ppb), $PM_{2.5}$ (R^2 = 0.65; RMSE: 3.65 μm/m^3), and O_3 (R^2 = 0.72; RMSE: 5.81 ppb).

Source-Oriented Chemical Transport Models for PM in California

Model Overview In the current study, the source-oriented chemical transport model developed by the University of California–Davis (UCD) and California Institute of Technology (CIT) (the UCD/CIT model [Chen et al. 2010; Kleeman et al. 1997, 2007; Kleeman and Cass 2001; Mysliwiec and Kleeman 2002]) was used to predict secondary PM concentrations over broad geographical regions at a 4 km × 4 km grid resolution. The primary chemical transport model developed by UCD (the UCD_P model [Hu et al. 2014a,b]) was based on the UCD/CIT model and tracked the detailed sources ($N \approx 900$) of primary particles but did not account for chemical reactions, gas-to-particle conversion, and any gaseous and secondary PM species produced by chemical reactions in the atmosphere. All the model simulations were conducted by Michael Kleeman's group at UCD. The model development work was funded by the EPA (Project R83386401) to study the use of regional transport models to estimate exposure to air pollution in epidemiology studies. From the EPA project, the existing models such as the EPA Community Multi-scale Air Quality model and the previous version of the UCD/CIT model were refined to provide source apportionment results in multiple size fractions for primary and secondary PM components. New models were developed to perform simultaneous source apportionment for 900 sources of primary PM. Details about the model development and evaluations are in Hu et al. (2015, 2014a,b) and the EPA Web site (*http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/8929*).

We prepared meteorological inputs for both the UCD/CIT and the UCD_P models using the Weather Research and Forecasting (WRF) model, version 3.1 (Skamarock et al. 2008). We described the size and composition of particle emissions using a library of primary-particle source profiles measured during actual source tests. We prepared gridded emissions using the raw emissions inventory provided by the California Air Resources Board (Hu et al.

2014a). Primary particles were assumed to be internally mixed; that is, all particles within a size bin were assumed to have the same composition. Both models were configured using a one-way nesting technique with a parent domain of 24 km horizontal resolution that covered the entire state of California and two nested domains with 4 km horizontal resolution that covered the most populated regions of Southern California, the San Francisco Bay Area, the San Joaquin Valley, and the southern portion of the Sacramento Valley. Over 92% of California's population lives in the 4 km domains, according to the most recent U.S. Census information.

UCD/CIT Chemical Transport Model of Secondary PM The UCD/CIT model includes a complete description of atmospheric transport, deposition, chemical reaction, and gas–particle transfer. The photochemical mechanism used by the model reflects the latest information from smog-chamber experiments. The Statewide Air Pollution Research Center Model 11 (SAPRC-11) photochemical mechanism (Carter and Heo 2012, 2013) was used to describe the gas-phase chemical reactions in the atmosphere. The SOA treatment was updated according to the method described in Carlton et al. (2010). A total of 12 semivolatile products and 7 nonvolatile products are formed from the oxidation of the precursor species. The gas–particle transfer of the semivolatile and nonvolatile products is dynamically calculated from the gas vapor pressures calculated over the particle surface and the kinetic limitations to mass transfer. The explicit chemical reactions and the parameters for the thermodynamic equilibrium calculation (i.e., enthalpy of vaporization, saturation concentrations, and stoichiometric yields) are provided in Carlton et al. (2010). The UCD/CIT model was configured with 16 vertical layers up to a height of 5 km above ground level, with 10 layers in the first 1 km. Particulate composition and mass concentrations were represented in 15 size bins, ranging from 0.01 to 10 μm in diameter.

Figure 1 shows the mean fractional bias (MFB) and mean fractional error (MFE) of total $PM_{2.5}$ mass, EC, OC, nitrate, sulfate, and ammonium using daily means across all measurement sites during a 9-year period (2000–2008). $PM_{2.5}$ total mass, EC, OC, and ammonium have MFBs within ±0.3 and MFEs less than 0.75, indicating general agreement between predictions and measurement for these species. Nitrate has an MFB of −0.4 but an MFE of 0.8, indicating that the daily predictions miss the extremely high and low concentrations. Sulfate has an MFB of −0.7 and an MFE of 0.8, indicating that it is consistently underpredicted.

UCD_P Primary Chemical Transport Model The UCD_P model applied in the current study separately tracked more than 900 individual sources with a unique emissions inventory code in the emissions database; formation of secondary PM was not considered, because of the additional computational burden associated with tracking this material on thousands of different primary particle cores (Hu et al. 2014a,b). The model processes only considered emissions, advection, diffusion, dry deposition, and wet deposition. The mass and density of size-resolved PM were tracked during model calculations, with composition profiles applied after the processing of results. The model was configured with 10 vertical layers up to a height of 5 km above ground level in Southern California and with 9 vertical layers up to 4 km above the ground level in the San Francisco Bay Area, the San Joaquin Valley, and the southern portion of the Sacramento Valley. Particulate composition and mass concentrations are represented in eight size bins, ranging from 0.01 to 20 μm in diameter.

For at least five sites, a comprehensive comparison of monthly mean model results and available measurements yielded Pearson correlation coefficients (r) ≥ 0.8 for elemental carbon (EC) and nine trace elements: potassium, chromium, zinc, iron, titanium, arsenic, calcium, manganese, and strontium in the $PM_{2.5}$ size fraction. Longer

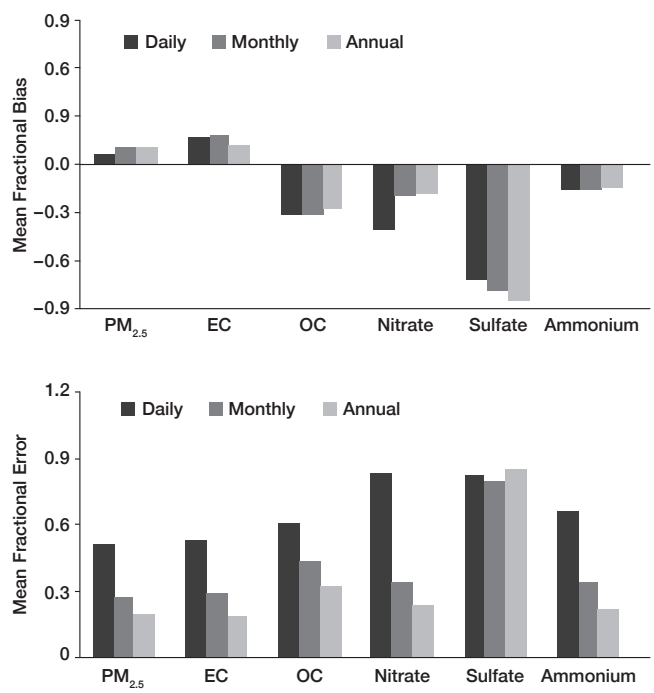


Figure 1. Evaluation of air pollution models in California, 2000–2008. Mean fractional bias (MFB) and mean fractional error (MFE) of particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) species when calculated using daily, monthly, and annual means. EC = elemental carbon; OC = organic carbon. (Source: Hu et al. 2015.)

averaging time increased the overall r^2 for $PM_{2.5}$ EC from 0.84 (1 day) to 0.96 (1 month) and increased the number of species with strong correlations at individual sites. Predicted $PM_{0.1}$ EC and $PM_{0.1}$ mass exhibited excellent agreement with observations (r^2 = 0.89 and 0.85, respectively) (Figure 2).

Predicted source contributions to primary $PM_{0.1}$ EC and $PM_{0.1}$ OC from the mobile, wood burning, and meat-cooking source categories generally agreed with the results from previous source apportionment studies using receptor-based techniques such as the chemical mass balance (CMB) model (Figure 3). The mobile source here included both traffic and offroad sources of burning gasoline and diesel fuel. Source prediction was also in good agreement with the CMB model for $PM_{2.5}$ mass. All sources were further subjected to a constraint check based on model performance for PM trace elemental composition. A total of 151 $PM_{2.5}$ sources and 71 $PM_{0.1}$ sources contained PM elements that were predicted at concentrations in general agreement with measured values at nearby monitoring sites. Significant spatial heterogeneity was predicted, and significantly different seasonal profiles were predicted for $PM_{2.5}$ and $PM_{0.1}$ between Central California and Southern California.

Exposure Estimation at Residential Locations In this study, the UCD/CIT model simulated both primary and secondary PM for years 2000–2008, whereas the UCD_P model simulated primary PM for years 2000–2006. In the epidemiological analysis, we kept only the sources for which satisfactory validation was obtained (gasoline, diesel, meat cooking, and wood burning) for primary PM (Hu et al. 2014b). Because of the significant underestimation in secondary PM mass, we did not use source information for secondary PM. We overlaid the maternal residences at the time of delivery with the modeling grids. Each subject was assigned the predicted concentrations at the grid she fell in. Daily concentrations were averaged to obtain exposure during specific pregnancy periods (entire pregnancy or first, second, or third trimester).

PAH Characterization and Modeling in Los Angeles

PAH Measurements In this study, we conducted field measurements of particle-bound polycyclic aromatic hydrocarbon (pPAH) for 2 days using filter samplers collocated with the portable EcoChem (League City, Texas) photoelectric aerosol sensor (PAS) samplers (1-minute resolution) in the Los Angeles Air Basin. Instrument failure (e.g., power outage, pump off, or incomplete PAS reading) occurred at 4 sites in the summer and 5 sites in the winter. In total, we obtained valid measurements at 19 sites in the summer (June–August 2011) and 18 sites in the winter (November 2011 to February 2012). Of the sampling sites, 10

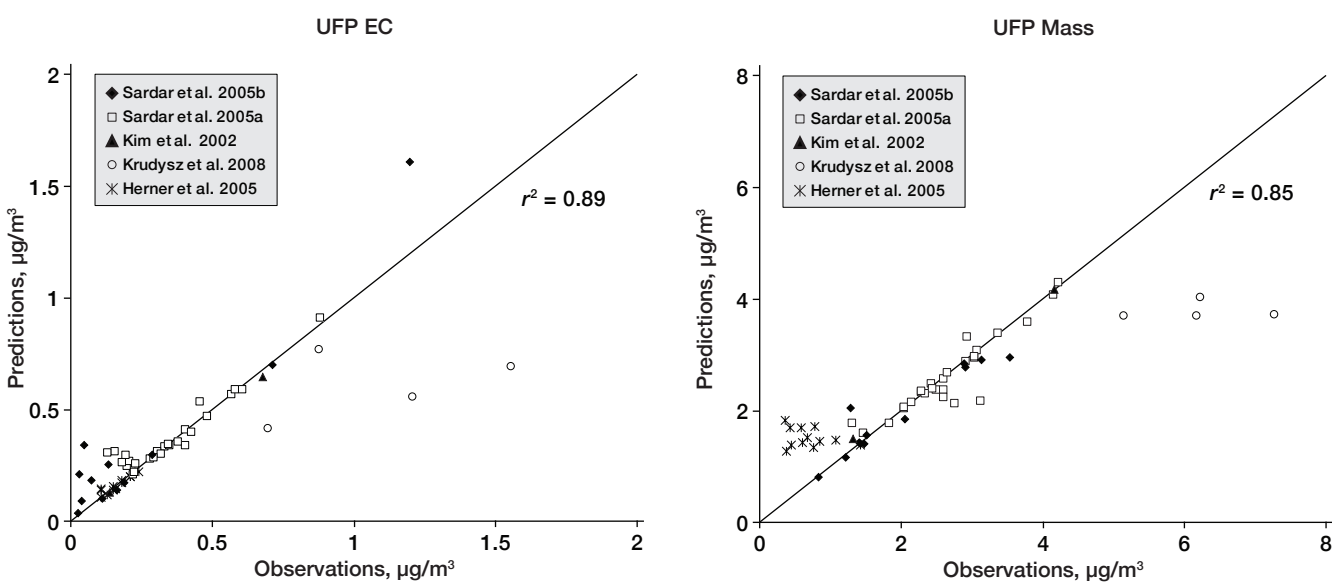


Figure 2. Observed and predicted averages of ultrafine particulate matter ($PM_{0.1}$) and quasi-ultrafine particulate matter ($PM_{0.18}$ and $PM_{0.25}$ [EC and mass]) in Southern California and Central California air basins, 2000–2006. Left, elemental carbon (EC); right, total mass. $PM_{0.1}$ was reported by Sardar et al. (2005a); $PM_{0.18}$, Sardar et al. (2005b); and $PM_{0.25}$, Krudysz et al. (2008). Averaging times were 1 month (Sardar et al. 2005a), 2 weeks (Sardar et al. 2005b), 5 months (Kim et al. 2002), 2.5 months (Krudysz et al. 2008), and 3 to 4 days (Herner et al. 2005). $PM_{0.1}$, $PM_{0.18}$, and $PM_{0.25}$ = particulate matter ≤0.1 µm, ≤0.18 µm, or ≤0.25 µm, respectively, in aerodynamic diameter. (Reprinted with permission from Hu et al. 2014a. Copyright 2014 American Chemical Society.)

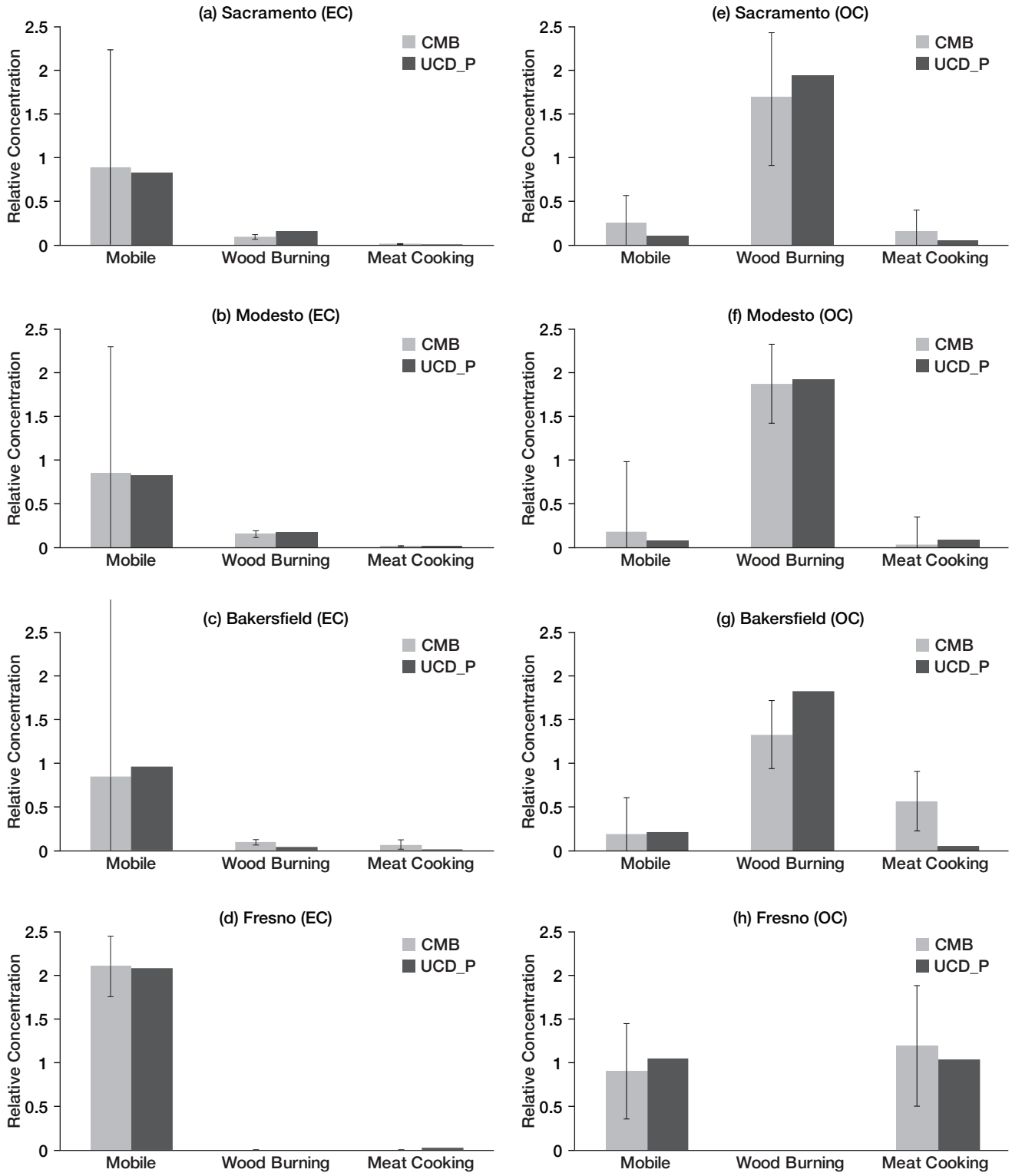


Figure 3. Relative source contribution to $PM_{0.1}$ elemental carbon (EC) (left panels) and organic carbon (OC) (right panels) predicted by the chemical mass balance (CMB) receptor model and the University of California–Davis/California Institute of Technology primary chemical transport model (UCD_P). Panels a, b, c, e, f, and g represent a winter episode in 2000; panels d and h represent a summer episode in 2006. (Reprinted with permission from Hu et al. 2014b. Copyright 2014 American Chemical Society.)

were routine EPA monitoring stations, and 9 were located just steps outside the homes of study volunteers (i.e., staff and their family and friends, whose homes were located in either high- or low-traffic areas). Because of the availability of samplers, only 2 sites were sampled at the same time.

In a previous project (R21ES016379) funded by the National Institute of Environmental Health Sciences (NIEHS), we collected 1-week gas-phase PAH samples using the Fan-Lloyd passive PAH sampler (Fan et al. 2006) in urban areas of south Los Angeles County and Orange County in 2 alternate weeks in the summer of 2009 (July 10–18 and July 24 to August 1) and the winter of 2009 (November 13–21 and December 4–12). The sampling sites were routine EPA monitoring stations and residential outdoor locations of a subset of pregnant women who enrolled in our prospective Air Pollution and Birth Outcomes Study. Overall, we obtained valid measurements at 39 sites in the summer and 36 sites in the winter of 2009. In addition to the gas-phase PAHs, we also collected collocated filter-based and PAS-measured pPAH concentrations at 2 or 3 EPA sites.

All the gas- and particle-phase PAH samples were analyzed by Dr. Tina Fan's lab at the Environmental and Occupational Health Sciences Institute at the University of Medicine and Dentistry of New Jersey, Rutgers University, using gas chromatography–mass spectrometry (GC–MS) assays. We analyzed 10 species for pPAH (naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo[*a*]anthracene, and chrysene) and 8 species for gas-phase PAH (naphthalene, acenaphthylene, acenaphthene, anthracene, fluorene, phenanthrene, fluoranthene, and pyrene). Total PAH concentrations were obtained by summing up the 10 species for pPAH and the 8 species for gas-phase PAH.

Correlations Between Filter-Based and PAS-Based pPAH Concentrations PAS-based 1-minute resolution data were matched to filter-based measurements by site and sampling time. In total, we collected collocated gas-phase PAH and pPAH data at 21 sites. The mean pPAH concentration ranged from 7.94 to 70.81 ng/m^3 from the PAS and 0.49 to 12.94 ng/m^3 from the filter-based measurements. The overall correlation between PAS and filter measurements for pPAH was 0.16 (*P* value: 0.40), indicating low correlation between PAS and filter measurements. Thus, the real-time PAS data cannot be used to reliably estimate total pPAH mass in our study region. It was not feasible to develop spatial models of pPAH mass concentrations, because of the limitations in this study, including the small number of filter-based pPAH measurements, nonsimultaneous data collection at most sites, and the poor correlation between filter and PAS measurements. Therefore, spatial models were only developed for gas-phase PAHs.

Spatial Model Development for Gas-Phase PAHs We analyzed data and developed models using the statistical language R 3.1 (Bell Laboratories, NJ). Because of a log-normal distribution, PAH concentrations were log-transformed before model development. Thiessen polygons (Appendix A [available on the HEI Web site], Figure A.1) were constructed around the sampling locations to derive spatial weight matrix that reflects spatial influence of neighbors. A spatial mixed regression model was constructed using spatial weight matrix and spatial covariates:

$$g(\hat{\mu}_u) = \mu_0 + \sum_{i=1}^{m} f_i\left(x_u^i, df\right) + \varepsilon^c$$

where μ_0 is the model intercept, $x_u^i \in X$ are the covariates, $f_i(\ldots)$ is the smooth function consisting of series basis functions (representing the nonlinear relationship), *df* is degrees of freedom that controls the smoothness of the curve fit, and *m* is the number of covariates. The variable *i* represents the index of the covariates (traffic index and meteorological parameters, etc.), *u* represents spatial location, and *c* represents spatial autocorrelation in the residual, $\varepsilon()$. For log-transformed concentrations, the link function is $g(\mu_u) = \mu_u, g(\hat{\mu}_u) \geq 0, \varepsilon^c \sim N\left(0, \Sigma^c\right)$, a spatial weight matrix. In other words, $\Sigma^c = \left[\sigma_{ij}^c\right]$ represents spatial autocorrelation that is incorporated into the model.

We examined the following spatial covariates in the model:

1. *Emission-related variables*: We calculated AADT traffic density and road length and distance to highways. Buffering decaying analysis was used to find the optimal buffer distance with the maximum Pearson correlation with PAH concentrations. We classified 2008 SCAG land-use types into five major categories: transportation, agriculture, parks and recreation, heavy industrial, and residential. We calculated the percentage of area for each land-use category within different buffer sizes (50 m to 15 km) around each sampling location. We calculated kernel population density in ArcGIS (version 10.0; ESRI, Redlands, CA) using block-level population data from U.S. Census 2000, a 5000 m search radius, and a 30 m resolution. Mean NDVI within a 150 m buffer was also extracted from the Landsat data. Distance to the nearest commercial cooking facility was also calculated from the 2008 InfoUSA data.
2. *Meteorological variables*: Hourly ambient temperature, relative humidity, wind speed multiplying sine

(wind direction), and wind speed multiplying cosine (wind direction) were averaged during the specific sampling periods using data from the nearest weather station. Using the modeled atmospheric stability class data from the National Oceanic and Atmospheric Administration, we classified the percentage of time under stable conditions.

We developed the model for the total concentrations of five PAH species (fluorene, phenanthrene, anthracene, fluoranthene, and pyrene) because they are heavier and more stable than the other three species (naphthalene, acenaphthylene, and acenaphthene) during the sampling process. Models were constructed separately for summer and winter. Leave-one-out cross-validation was employed for model evaluation.

In total, we collected four weekly PAH concentrations at 36 to 39 sites. There was a remarkable difference (16.7 ng/m^3 vs. 31.7 ng/m^3) between summer and winter concentrations. Higher spatial variability was observed in the summer than in the winter (ratio of standard deviation to mean concentration: 0.63 for summer; 0.47 for winter). In the summer, emissions from traffic and commercial cooking facilities were significantly correlated with PAH levels; in the winter, traffic, other emission-related factors (i.e., high-density residential land use, agriculture land use, and park and recreational land use), and temperature were significantly correlated with PAH.

Table 2 shows the final multivariable models we developed to predict seasonal gas-phase PAH concentrations. This was one of the first studies that developed models to estimate gas-phase PAH concentrations by season in a large metropolitan area. Leave-one-out cross-validation R^2 was 0.61 in the summer and 0.79 in the winter. In the summer, spatial autocorrelation, emission-related variables (roadway length, population density, and distance to commercial cooking facilities), and meteorological variables (temperature and wind speed), accounted for 24%, 29%, and 15% of the variance in PAH concentrations, respectively. In the winter, spatial autocorrelation and traffic density accounted for approximately 45% and 32% of the variance in PAH concentrations, respectively, whereas meteorological variables contributed less than 4% to the overall variance explained. PAH concentrations were more affected by traffic emissions in the winter than those in the summer.

Exposure Estimation at Residential Locations We estimated annual mean PAH exposure in Los Angeles County for about 1.1 million subject locations. To construct the spatial weight matrix, we established the relationship of spatial topology by overlaying the subject locations to be estimated with the Thiessen polygons of the sample data. If there was no polygon covering a subject location, we assigned the closest polygon to the subject location.

Spatiotemporal Modeling of NO_2 in Los Angeles

Modeling Approach We developed a two-stage hierarchical model to capture spatiotemporal variability of NO_2 concentrations in Los Angeles County and Orange County by combining high-temporal-resolution data from routine monitoring stations with high-spatial-resolution data from investigator-initiated episodic measurements. Detailed descriptions of the model development can be found in Li et al. (2013). We summarize the main model structure below.

For the current work, the model was based on 2000–2009 measurements of NO_2 in Los Angeles County and Orange County. We applied the 75% data completeness criterion to select EPA routine monitoring stations with long-term weekly air-quality measurements. Iterative singular value decomposition was used to fill in missing weekly concentrations for the long-term time-series data (Appendix A, Table A.1). Episodic measurements included 161 valid samples from University of California, Los Angeles (collected in 2 continuous weeks, September 16 to October 1, 2006, and February 10–25, 2007) and 32 valid samples from

Table 2. Multivariable regression models for total polycyclic aromatic hydrocarbon (PAH) concentrations[a]

Season	Predictors (variance explained)	R^2 of the model	Leave-one-out cross-validation R^2
Summer	Spatial autocorrelation effect (24%); distance to commercial cooking facilities (5%); ambient temperature (10%); ambient wind speed (5%); population density (6%); road length within the buffer of 700 m (18%)	0.68	0.61
Winter	Spatial autocorrelation effect (44.6%); traffic density (31.8%); ambient temperature (2.7%); ambient wind speed (1%)	0.80	0.79

[a] Total PAH includes fluorene, phenanthrene, anthracene, fluoranthene, and pyrene.

University of California–Irvine, collected at outdoor home locations of subjects in south Los Angeles County and Orange County for 4 weeks in 2009 (July 10–18, July 24 to August 1, November 13–21, and December 4–12).

In stage 1, normally distributed log-transformed NO_2 concentrations from EPA's routine monitoring stations were decomposed into the sum of a systematic mean component and residual. The mean spatiotemporal field typically represents the dominant seasonal or long-term trend of concentrations for the study domain (Szpiro et al. 2010). Using the empirical orthogonal functions, we further divided the mean spatiotemporal field into one constant and two independent temporal basis functions. Temporal basis functions represented the leading modes of temporal variability of air pollutant concentrations for the study region. The coefficients for temporal basis functions represent spatial variability of such temporal variability modes and were modeled in stage 2. In this study, we derived only the first three temporal basis functions and their spatially varying coefficients for two reasons. First, the product of the first three temporal basis functions can usually capture the majority of spatiotemporal variability of pollutant concentrations (Lindstrom et al. 2011; Szpiro et al. 2010). Second, we only had up to four weekly measurements for episodic measurements, although a minimum of three is needed to derive three temporal basis functions and their associated coefficients.

In stage 2, we applied a nonlinear generalized additive model in R (version 2.11.1) to model the spatially varying coefficients of temporal basis functions to estimate these coefficients at the new locations using the following spatial variables:

1. *Emission-related parameters*: The parameters included three variables: (1) roadway length inversely weighted by the distance to the sampling location; (2) the shortest distances to each of four roadway types (highway, primary roads, secondary or connecting roads, and local roads); and (3) AADT weighted by roadway length. The 2001 SCAG land-use types were classified into five major categories: transportation, industry, agriculture (including open space and vacant), commercial, and residential. We calculated the percentage of area for each land-use category within an optimal buffer size.
2. *Long-term meteorology*: We estimated long-term (2006–2009) mean values of temperature, relative humidity, precipitation, wind speed multiplying sine (wind direction), and wind speed multiplying cosine (wind direction).
3. *Others*: Each sampling location was assigned 10 m resolution elevation and the shortest distance to the shoreline.

Finally, we modeled spatial residuals in stage 1. The residuals were assumed to be spatially correlated after removal of temporal autocorrelation and were modeled by co-kriging them with regional residuals at nearby sampling sites with the assumption of a stable spatial domain after removal of local means (Christakos 1990). Our model had several improvements over a similar hierarchical modeling approach (Lindstrom et al. 2011; Szpiro et al. 2010): a nonlinear generalized additive model (GAM) to estimate spatial coefficients of the temporal basis functions, the incorporation of regional residuals through co-kriging, and additional spatial covariates, including long-term meteorology.

Exposure Estimation at Residential Locations To predict exposure in this study, we extended the long-term EPA samples to earlier years (2000–2006) and applied the aforementioned spatiotemporal models using data from January 3, 2000, to December 28, 2009. We selected the sites with ≥ 75% complete measurements (52 sites for NO_2; 55 sites for all nitrogen oxides [NO_x]) for California. Additional model evaluation was conducted through leave-one-out cross-validation. Total r^2 for all the time series of the 25 sites was 0.72 for the measured values but much higher (0.90) for the smoothed curves of the measurements. Figure 4 compares measured values, smooth curve of the measurements, and modeled concentrations at one EPA monitoring station. The total r^2 for long-term means for 25 sites from 2000 to 2009 is 0.95 (RMSE = 1.73 ppb). The Pearson correlation coefficient of the estimates of time series with the observed values ranged from 0.84 to 0.91 across the 25 sites.

Using this updated model, we estimated weekly concentrations of NO_2 from 2000 to 2009 for all the residential locations in Los Angeles County. In the prediction, we restricted the extreme values of the spatial covariates to ensure that the model does not predict unrealistically high or low values. Mean exposures during specific exposure windows (the entire pregnancy and the first, second, and third trimesters) were calculated for each subject.

CAlifornia LINE Source Dispersion Model Version 4 for Carbon Monoxide, NO_x, and UFP Number

We used a modified version of CAlifornia LINE Source Dispersion Model Version 4 (CALINE4) (Benson 1989; Wu et al. 2009a,b) to predict ambient concentrations of two surrogates of traffic-generated air pollution (carbon monoxide [CO] and NO_x) from local traffic emissions and UFP

numbers up to 3 km from maternal residences. Input data for the prediction process included roadway geometry, traffic counts, emission factors, and meteorological parameters (wind speed, wind direction, temperature stability class, and mixing heights). CALINE4 predictions in this study did not incorporate background levels of pollutants and thus solely represent the contribution from local traffic emissions.

Because the original CALINE4 was not able to simulate UFP number concentration, we have developed distance-dependent scaling functions within the CALINE4 model to predict particle number concentrations near roadways (Yuan et al. 2011). We developed the scaling functions by comparing measured UFP (6–220 nm) concentrations near highways in California and Texas with the corresponding UFP concentration estimates from the original CALINE4 model, with no adjustment. The model was used to predict UFP concentrations for additional near-freeway locations, and the modeled concentrations agreed well with measurements ($r > 0.92$) (Yuan et al. 2011). In the current work, we further evaluated the predicted and measured concentrations at four retirement community sites in the Los Angeles area with extended sampling time (NIEHS/NIH grant no. ES-012243; Ralph Delfino, principal investigator). Results showed a moderately strong correlation between measured and predicted concentrations ($r = 0.75$) for 357 daily UFP concentrations (Appendix A, Table A.2).

We used Caltrans roadway and AADT counts as described earlier. Day of week and diurnal variability of traffic counts were added by scaling the AADT by weekday or weekend and diurnal profile (24 hours) of traffic. Although this profile was derived from summarized statistics of freeway measurements, we applied it to both highways and major surface streets because no reliable data were available for the temporal variability of traffic on specific surface streets in the large study region.

Year and season (winter and summer) specific emission factors for CO and NO_x were obtained from the EMFAC2011 vehicle emissions model (California Air Resources Board 2013). We developed the following equation to estimate UFP emission factors using 32 observations from published studies (Yuan et al. 2011):

$$\log_{10}(\mathrm{EF}) = (0.92 \times \mathrm{HDF}) + (0.0089 \times \mathrm{VS}) + 13.64 \quad (r = 0.64),$$

where EF is the emission factor of UFP number concentration (expressed as UFPs per vehicle-kilometer); HDF is the percentage of heavy-duty vehicles; and VS is vehicle speed (kilometers per hour).

After considering the frequency distribution and the sampling setting (e.g., the height of the sampler), we decided to use data collected by the EPA and the National Interagency Fire Center for the CALINE4 model. We kept the sites whose valid data was at least 75% complete for wind speed, wind direction, and temperature. Because we included more than 4 million subjects in this study, we used a frequency-based approach rather than modeling real-time hourly meteorology. Specifically, for each subject, we modeled 576 unique meteorological conditions

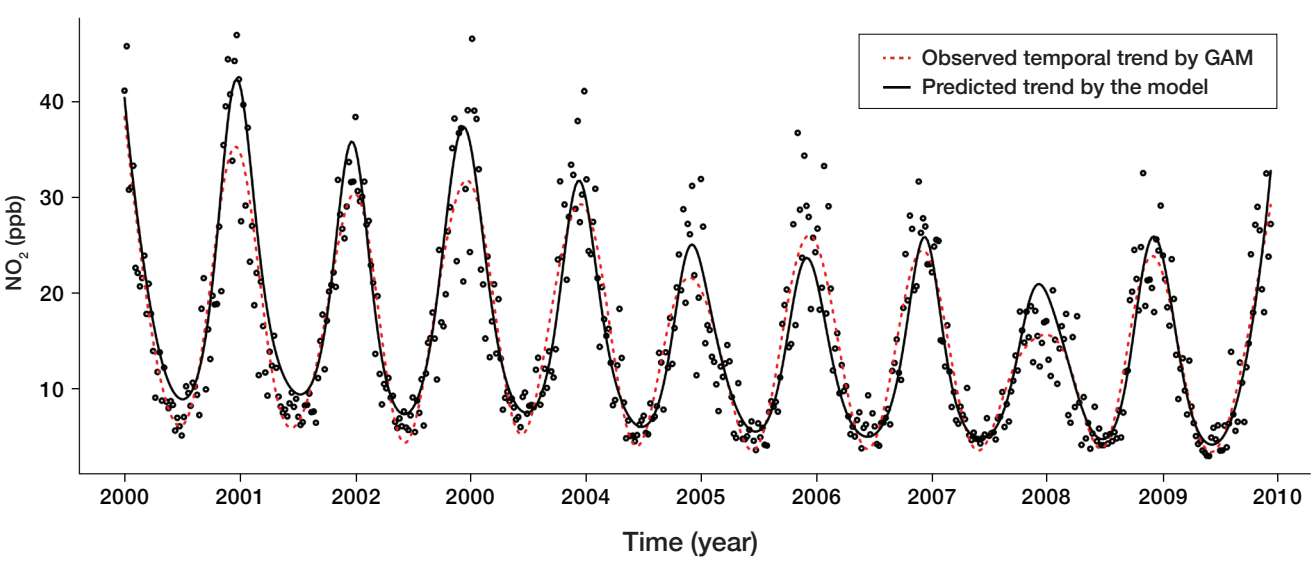


Figure 4. Observed vs. predicted trend for NO_2 at an EPA air-monitoring site in Costa Mesa, California, 2000–2009. GAM = generalized additive model.

that were classified by season (warm and cold), time of day (night, daytime with limited mixing, and daytime with good mixing), wind speed (six categories: ≤ 1, 2, 3, 4, 5.5, ≥ 7.5 m/sec), and wind direction (16 categories: 0 to 360 degrees, with a 22.5-degree interval). We also calculated distance between each residence and the 10 closet meteorological stations. With priority given to the closest station with valid measurement data, we assigned hourly meteorological data to each subject. If data were missing at the nearest station, the next nearest station was examined until valid data were available. Then, hourly meteorological data for each subject were classified into the 576 unique meteorological cases, and frequency tables were generated by pregnancy periods (the entire pregnancy and the first, second, and third trimester). Finally, the CALINE4 model outputs for the 576 meteorological cases were weighted by the frequency with which these meteorological conditions occurred in the corresponding periods for each subject.

Traffic Index

We calculated three types of traffic indicators: traffic density, road length, and distance to roadways. Traffic density was defined as the mean number of vehicles per day per meter of road segment. It was calculated by weighting the annual mean daily traffic counts by the length of the street segments within four buffering distances (i.e., 50 m, 150 m, 250 m, and 350 m) of each residence. We used 2002 Caltrans AADT data, which included highways, and major roads, and scaled these data to other years according to the yearly trend of vehicle miles traveled, as we described earlier.

Roadway length and distance to roadways were estimated using the 2005 TeleAtlas data that were bundled with the ESRI ArcGIS software. Road types were characterized by the functional road class (FRC) that describes the functional importance of roads within the transportation network (Tele Atlas 2010). The following six FRCs were used in this study:

0: Motorway, freeway, or major road

1: Major road less important than a motorway, used for international and national traffic and transport

2: Other major road, used to travel between different neighboring regions of a country

3: Secondary road, used to travel between different parts of the same region

4: Local connecting road, used to make settlements accessible or parts of a settlement accessible

5: Local road of high importance, used as the main connection in a settlement

Local roads (FRC 6 through 8) were not included.

We derived the following traffic index indicators using the 2005 TeleAtlas data:

- Length of the roadways within the buffering distances of 50 m, 150 m, 250 m, and 350 m of the subject's residence for all the roadways in FRCs 0 through 5
- Shortest distances from the subject's residence to all the roadways in FRCs 0 through 5

BIRTH RECORD DATA

Geocoding

Birth certificate records for all births occurring from January 1, 2001, to December 31, 2008, in California (N = 4,385,997) were obtained from the California Department of Public Health. Maternal addresses of residence recorded on birth certificates were geocoded using the University of Southern California GIS Research Laboratory geocoding, which geocoded births at the centroid of tax parcels whenever feasible (Goldberg 2011a, 2011b). If an address could not be matched to a parcel, we interpolated the street segment using linear-based feature interpolation (Goldberg 2011b). The line on the correct side of the street segment was examined from the beginning to the end, and the number of addresses on that segment was counted. We derived the latitude and longitude coordinates of an address at the correct distance from the beginning of the street segment, assuming even distribution of known locations and with a static 10 m dropback orthogonal to the direction of the street segment.

Of the total birth certificate records used, 54.02% (n = 2,369,104) had addresses that could be geocoded to within a parcel, and 14.14% (n = 620,092) could be geocoded to the exact centroid of a parcel. Further, 37.23% (n = 1,633,012) could be geocoded to within 50 m of a parcel. In addition, 8.55% (n = 375,008) of addresses were in California but not within or close to a parcel; they were geocoded to the centroid of the zip code or city whenever feasible. The mean zip code area was 240 km^2 (0.15–9311 km^2) for all the zip code areas in the entire state of California (1707 areas) and was 134 km^2 (0.15–3897 km^2) for the zip code areas whose centroids were covered by the UCD_P modeling domain (1359 areas). In total, 1361 births had no usable coordinates at all, and 7512 infants were born to women residing outside California. After excluding these births and those missing the state file number information (n = 8119, partly overlapping the births that lacked usable coordinates or that occurred outside California), we obtained 4,370,371 pregnancy records.

Multiple births (n = 132,369) were excluded, as were infants with recorded birth defects or unknown birth defects status (n = 18,811 and n = 675, respectively). Birth records lacking information for gestational age (n = 196,247), reporting estimated gestational age shorter than 121 or longer than 319 days (n = 2051 and n = 41,017, respectively), or recording implausible combinations of birth weight and gestational age (n = 17,026) (Alexander et al. 1996) were excluded from the main analyses. Further, infants born from mothers older than 60 years (n = 43) were excluded. Several exclusion criteria overlapped for certain births, leaving 3,972,594 births from the source population eligible for the study.

Description of the Population

Table 3 describes the source study population. The mean length of gestation was 275.1 days (median: 276, standard deviation [SD]: 15.24). In total, 9.94% of infants were born preterm. The mean birth weight for term birth infants was 3420.64 g (median: 3402 g, SD: 462.86 g), and 2.05% of them had a LBW. Preeclampsia was reported on 1.96% of birth certificates. GDM was mentioned only on 2006–2008 birth certificates and was reported on 3.06% of them.

Data on prepregnancy BMI, gestational weight gain, and smoking were recorded only on 2007–2008 birth certificates. Prepregnancy BMI and gestational weight gain were the variables with the largest amount of missing data; 10.48% and 10.43% of the certificates, respectively, were missing these data. Maternal education level was missing for 2.45% of the subjects, and the percentage of missing data was even lower for other variables. However, the true percentage of missing data for diabetes, chronic hypertension, and preeclampsia is unknown: only the presence, but not the absence, of these diseases was explicitly recorded on birth certificates. Still, we coded a few subjects' records as "missing data" when the records noted that a disease had occurred but there was no mention of the nature of the disease.

Table 4 shows the incidence of pregnancy outcomes by year of birth. There was no monotonic temporal trend in the outcomes (except for GDM, which showed an increase, but this outcome was reported only for the years 2006–2008).

Comparison of Birth Certificate Data and Hospital-Based Birth Records on the Reporting of Pregnancy Complications

From a previous NIEHS-funded project (R21ES016379), birth records from 2001 to 2006 (N = 66,352) were obtained from the Memorial Care System, a Southern California network of four hospitals (Anaheim, Long Beach, Orange Coast, and Saddleback) that maintain a perinatal database for research purposes (Wu et al. 2009b). Memorial Care birth records were matched to birth certificate data using fuzzy matching logic through the SAS COMPGED function. This function measures the "generalized edit distance," which represents the degree of difference between two text strings. Memorial Care records were matched to birth certificate records according to their calculated degree of similarity for different combinations of four variables: mother's first and last name, child's date of birth, mother's date of birth, and hospital of delivery. Using relatively stringent matching criteria, we matched a total of 62,200 records (94%) from the Memorial Care database to birth certificates. We hypothesized that the Memorial Care data on pregnancy complications would be of better quality because the hospital data came from a research database that underwent more stringent quality check by research nurses.

Compared with Memorial Care data, birth certificates significantly underreported the incidence of preeclampsia (1.4% vs 3.1%) and all types of diabetes (2.0% vs. 5.6%), respectively. We calculated the ratio of the incidence of preeclampsia and diabetes (including both preexisting diabetes and GDM) recorded on birth certificates to the same conditions' incidence reported on Memorial Care records. Thus, the smaller the ratio, the greater the underreporting on the birth certificates. We then examined whether the underreporting on birth certificates was disproportionately distributed among different SES groups or racial or ethnic groups. For preeclampsia, the underreporting ratio was 0.47 for women with college or higher education and 0.39 for women with high school or lower education; the difference was statistically significant, according to a permutation test (P = 0.01). We also observed a lower ratio (i.e., greater underreporting) of preeclampsia in Hispanic women than in non-Hispanic white women (P = 0.01) and in women with public insurance than in those with private insurance (P = 0.02). For diabetes, a similar pattern was found. A statistically significant lower ratio of diabetes was observed in Hispanic women, women with high school or lower education, and women with public insurance. These results indicated a problem of underreporting of pregnancy complications for low-SES groups in birth certificate data.

STATISTICAL METHODS AND DATA ANALYSIS

The study received approvals from the human subject protection boards of the University of California–Irvine and the California Health and Human Services Agency.

Table 3. Characteristics of the study population of pregnant women, from California birth certificates, 2001–2008

	Subjects	Percent
2001–2008 birth certificate data (N=3,972,594)		
Maternal race/ethnicity		
Asian	460,311	11.59
Black	208,352	5.24
Hispanic	2,039,545	51.34
Caucasian	1,129,431	28.43
Multiple/other	89,883	2.26
Missing	45,072	1.13
Maternal age (years)		
<15	5,032	0.13
15–19	371,806	9.36
20–24	906,453	22.82
25–29	1,047,819	26.38
30–34	971,822	24.46
35–39	537,622	13.53
40–44	124,995	3.15
45–49	6,605	0.17
≥50	440	0.01
Maternal education		
Lower than 8th grade	414,980	10.45
9th grade to high school	1,755,297	44.19
College (<4 years)	788,235	19.84
College (≥4 years)	916,891	23.08
Missing	97,191	2.45
Median income per census block group		
≤$30,933	983,294	24.75
$30,938–$42,483	991,190	24.95
$42,500–$60,179	993,728	25.01
$60,185–$200,001	991,892	24.97
Missing	12,490	0.31
Parity		
Primparous	1,570,415	39.53
Multiparous	2,400,613	60.43
Missing	1,566	0.04
Trimester during which primary care began		
None	16,175	0.41
1	3,390,359	85.34
2	452,398	11.39
3	86,737	2.18
Missing	26,925	0.68
Diabetes (total)		
No	3,857,232	97.10
Yes	115,190	2.90
Missing[a]	172	0
Chronic hypertension		
No	3,958,030	99.63
Yes	14,392	0.36
Missing[a]	172	0
Preeclampsia		
No	3,894,582	98.04
Yes	77,971	1.96
Missing[a]	41	0
Preterm birth		
No	3,577,911	90.06
Yes	394,683	9.94
Low birth weight		
No	3,776,774	95.07
Yes	195,820	4.93
2006–2008 birth certificate data (N=1,550,330)		
Gestational diabetes		
No	1,502,804	96.93
Yes	47,479	3.06
Missing[a]	47	0
2007–2008 birth certificate data (N=1,030,411)		
Prepregnancy body mass index		
≤19.9	69,761	6.77
20–24.9	390,772	37.92
25–29.9	111,023	10.77
30–34.9	238,757	23.17
≥35	112,139	10.88
Missing	107,959	10.48
Weight gain during pregnancy, in kg		
<5	72,616	7.05
5–9.9	189,322	18.37
10–14.9	308,341	29.92
15–19.9	218,016	21.16
≥20	134,640	13.07
Missing	107,476	10.43
Smoking during pregnancy		
No	1,004,731	97.51
Yes	25,680	2.49

[a] The true proportion of missing data for diabetes, chronic hypertension, and preeclampsia is actually unknown. Only the presence, but not the absence, of these diseases was explicitly recorded on birth certificates. Still, a few data were coded as "missing" for these conditions when the presence of the disease was mentioned but its nature was not specficied.

Table 4. Incidence of pregnancy outcomes by year of birth (%) in California birth certificates

	2001	2002	2003	2004	2005	2006	2007	2008
Preterm birth	9.63	9.65	9.89	9.99	10.16	10.1	10.21	9.79
Term low birth weight	1.99	1.97	2.06	2.07	2.08	2.18	2.03	2.01
Preeclampsia	2.07	1.99	1.84	1.97	2.11	1.93	1.88	1.92
Gestational diabetes mellitus	NA	NA	NA	NA	NA	2.95	3.11	3.13

Term Low Birth Weight

For term LBW analyses, infants born preterm (n = 394,683) were excluded from the source population of 3,972,594 birth records. Infants born after 308 days of gestation (44 weeks, n = 43,203) were further excluded, for consistency with other major studies weight (Bell et al. 2010, 2012; Darrow et al. 2011; Ebisu and Bell 2012). In the remaining source population of 3,534,708 term birth records in the entire state of California (2001–2008), 72,632 cases of LBW were identified and included in the study. For the purpose of the main analysis, five controls (term-born children weighing ≥ 2500 g at birth) per case were randomly selected from the source population of potential term-birth controls. The resulting case-control data sets were analyzed by logistic regression with random effect per hospital using generalized additive mixed models in the mgcv package of the R environment (version 3.0.1). The main models were adjusted for race/ethnicity and educational level as categorical variables, and for maternal age and median household income (at census block-group level) using penalized quadratic splines with basis dimension of 2.

We introduced air pollution indicators as linear terms in the models. For air pollution indicators that represent ambient concentration of air pollutants, we reported related odds ratios (ORs) for term LBW for an interquartile range (IQR) increase of air pollutant concentrations, allowing for a more straightforward comparison of effect sizes between different air pollution indicators. To simplify the quantitative comparison of associations between term LBW and traffic density or road length across buffers of different sizes, ORs for these indicators were expressed per increase of 10,000 vehicles per day per meter for traffic density and 100 m for road length. We analyzed distance to roadway using dichotomous indicators for living or not living within certain distances from roads.

For analyses by subgroup (i.e., SES and other maternal factors), 10 controls were randomly selected per case to avoid, as much as possible, convergence problems in small subgroups (e.g., women with chronic hypertension or diabetes). For subgroup analyses based on variables only available in years 2007–2008 (smoking, BMI, and gestational weight gain), all potential controls had to be selected for the same reason (to avoid convergence problems as much as possible). For a proper comparison of the magnitude of associations between subgroups, whenever air pollution indicators represented ambient concentration of air pollutants, ORs for each subgroup were standardized to the IQR in exposure observed in the entire population. The standardization of ORs for traffic density, road length, and distance to roads was the same in the subgroup analyses as it was in the main analyses. To test whether associations between air pollution and pregnancy outcomes significantly differed across k subgroups defined by categories of potential effect modifiers (in other terms, to test whether there were significant interactions between air pollution and these factors on the risk of pregnancy outcomes), heterogeneity tests based on the chi-square statistic with $k - 1$ degrees of freedom were used (Paul and Donner 1989).

Preterm Births

All PTB cases (N = 394,683) from the source population were included in the PTB study. For each PTB case, two controls (infants born at 37 or more gestational weeks) matched on the year of conception were randomly selected from the source population. Selecting two controls per case proved sufficient (both for the main and for the subgroup analyses) because of the relatively large number of PTBs (9.9%, compared with only 2.1% for term LBW). For each control, we truncated exposure estimates at the gestational age reached by the PTB case to which it had been matched. To account for this risk set design, conditional logistic regression was employed for the analysis of the association between air pollution and PTB, using the survival package of the R environment (version 3.0.1). Robust standard errors were estimated (Lee et al. 2013). The main models were adjusted for race/ethnicity and educational level as categorical variables, and for maternal age and median household income (at census block-group level) using quadratic polynomial functions.

For the purpose of subgroup analyses, controls were matched to cases on both the year of conception and the level of the variable considered for stratification (e.g., same education level or smoking status). Beyond these specificities, the methods used for analyses and the presentation of results were the same as for the term LBW analyses described above.

Preeclampsia

Starting from the source population of 3,972,594 births eligible for the study, all preeclampsia and eclampsia cases identified for 2001–2008 were included in the preeclampsia study. As in other studies (Pedersen et al. 2014), we grouped preeclampsia and eclampsia cases in a single variable called "preeclampsia" (n = 77,971). The methods used for statistical analyses were the same as to those described for the term LBW analyses, except that the source population was not limited to term births.

Gestational Diabetes Mellitus

GDM was reported separately from prepregnancy diabetes in California birth certificates for the first time in 2006. Therefore, only 3 years of data (2006–2008) could be included for the GDM analyses. Over this period, 1,550,330 birth certificates matched the criteria defined for inclusion in the study. GDM (N = 47,479) cases were included in the analyses after omitting cases with multiple births, recorded birth defects or unknown birth defects status, missing information for gestational age, estimated gestational age shorter than 121 or longer than 319 days, implausible combinations of birth weight and gestational age, and mothers older than 60 years. Again, the methods used for statistical analyses were the same as those described for the term LBW analyses, except that the source population was not limited to term births.

Adjustment for Confounders

Figure 5 summarizes in a causal diagram our prior knowledge about the relationships between the potential confounding variables in studies of the associations between air pollution and the pregnancy outcomes of interest. The causal diagram theory (Greenland et al. 1999) warns against adjusting for potential colliders, which are factors determined by two or more other factors already included in the model (e.g., parity or smoking, both of which are partly determined by maternal age and socioeconomic factors), to avoid overadjustment bias.

In light of our causal diagram (Figure 5), the statistical models we used for the main analyses were adjusted for a simple set of potential confounders for each outcome, namely, maternal age, race/ethnicity, education, and neighborhood socioeconomic conditions. All four confounders are strong and well-documented risk factors for the four pregnancy outcomes we studied. In addition, these confounders are probably among the most accurately reported variables in birth certificates and are determinants of some maternal behaviors (e.g., smoking), parity, and access to prenatal care. They are also associated with air pollution levels (see Appendix A, Tables A.6 to A.9) and with the risk of some chronic diseases (hypertension, diabetes) or suboptimal health status (e.g., obesity), all of which in turn are also documented risk factors for the pregnancy outcomes we studied. However, because we acknowledge possible uncertainties in our causal diagram and in the selection of the potential confounders used in the analyses (maternal age, race/ethnicity, education, and neighborhood socioeconomic conditions), we examined the influence of adjusting for other risk factors as part of sensitivity analyses.

RESULTS

In this report, we consider the mean exposures during the entire pregnancy as the exposure of primary interest. Results for specific exposure periods are summarized in this section, but detailed data for each adverse pregnancy outcome are presented in the appendices. We present summary statistics for the distribution of air pollution exposures during the entire pregnancy (Appendix A, Table A.3) and the long-term trends of exposures by year of birth during the study period (Appendix A, Table A.4). The correlation matrix for exposures to major air pollutants is shown in Appendix A, Table A.5 (traffic index and UCD_P modeled concentrations were omitted in this table because of space limitations). The distributions of the mean air pollutants exposures by the categories of potential effect modifiers (e.g., maternal age, education, race/ethnicity, household income) are summarized in Appendix A, Tables A.6 through A.13.

TERM LOW BIRTH WEIGHT

When exposure averaged over the entire pregnancy was considered, term LBW was positively associated with EBK-interpolated measurements of O_3 (OR per IQR in exposure: 1.035; 95% CI: 1.017–1.054) but not of total $PM_{2.5}$ or NO_2 (Table 5).

No significant association was observed between term LBW and primary $PM_{2.5}$ or $PM_{0.1}$ from all sources grouped

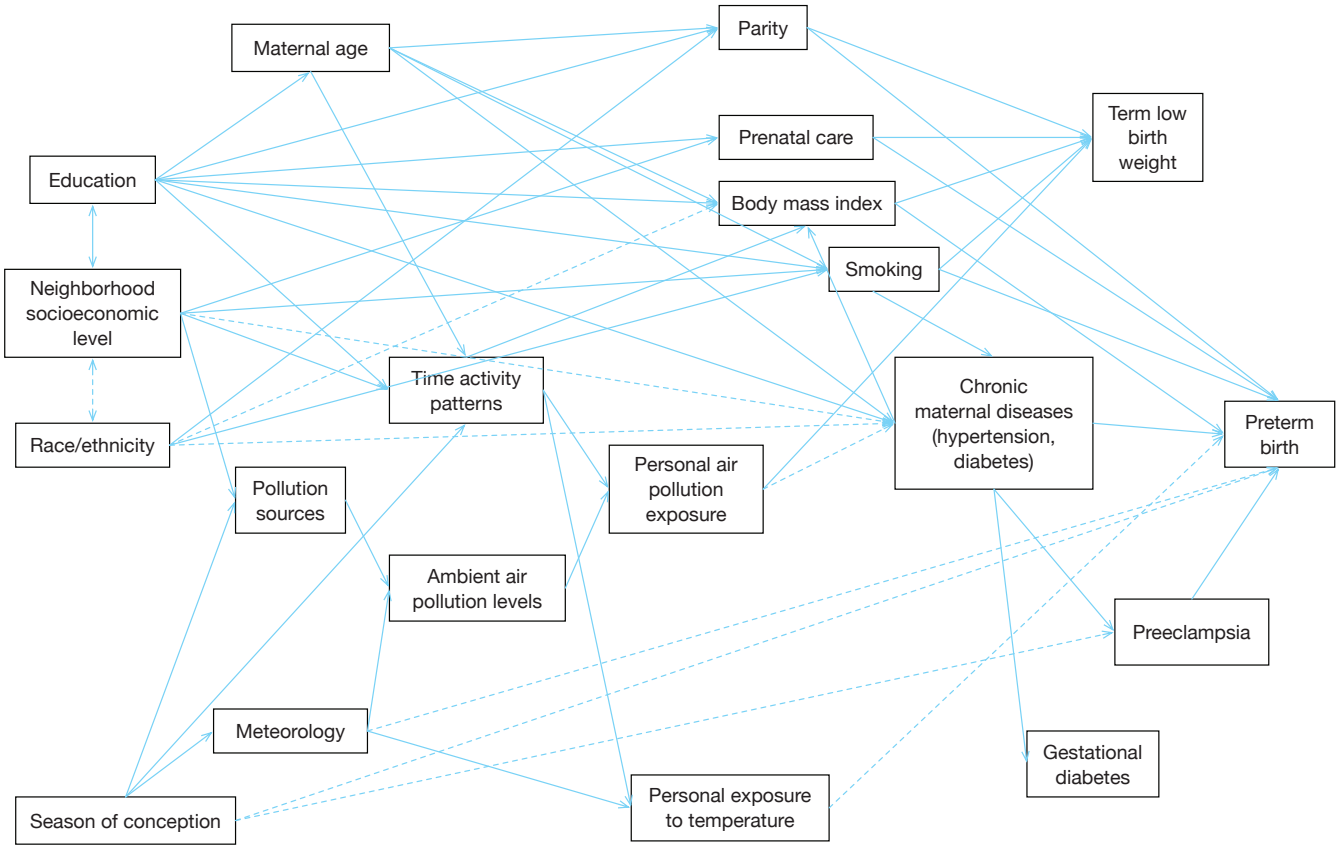


Figure 5. Directed acyclic graph of assumed relationships between preterm birth, air pollution, and other risk factors, based on literature data. Dotted lines represent relationships for which a greater degree of uncertainty exists (observations based on a few studies and that would call for confirmation by more studies, or for which mechanisms are not well understood).

together, modeled at a 4 km × 4 km resolution. However, term LBW risk was positively associated with primary $PM_{2.5}$ and $PM_{0.1}$ emitted by onroad gasoline vehicles (OR per IQR in exposure for $PM_{0.1}$: 1.051; 95% CI: 1.015–1.089), onroad diesel vehicles (OR per IQR in exposure for $PM_{0.1}$: 1.030; 95% CI: 1.000–1.060), and commercial meat cooking (in $PM_{0.1}$ only). Associations were slightly weaker for the $PM_{2.5}$ than for the $PM_{0.1}$ fraction but still statistically significant for onroad gasoline and diesel vehicles. Conversely, primary PM from wood burning (both in the $PM_{0.1}$ and the $PM_{2.5}$ fractions) was inversely associated with term LBW risk. Still, at the 4 km × 4 km modeling resolution, a significant positive association was observed for only one chemical component, namely, for SOA in $PM_{0.1}$. However, positive associations were close to significance for SOA and nitrates in $PM_{2.5}$.

No significant association was observed between term LBW and PAH (modeled by the spatial model in Los Angeles County only). Convergence was not reached for NO_2.

When we modeled primary emissions from local traffic at a fine geographical resolution using CALINE4, we found no association between term LBW and UFP number, CO, or NO_x in the entire population (Table 5). However, when analyses were restricted to the population in which maternal addresses could be geocoded most accurately (i.e., at the exact parcel centroid), all three pollutants were positively associated with term LBW (Appendix B [available on the HEI Web site], Table B.1). The association was significant for UFP number (OR per IQR in exposure: 1.031; 95% CI: 1.006–1.056) and close to significance for NO_x (OR per IQR in exposure: 1.024; 95% CI: 0.999–1.050).

When simpler indicators of traffic exposure were considered, term LBW was significantly associated with road traffic indicators within 50 m from maternal homes: traffic density (OR per 10,000 vehicles per day per meter: 1.124; 95% CI: 1.040–1.214) and total road length (OR per 100 m of cumulated road length within the buffer: 1.037; 95% CI: 1.020–1.054).

Table 5. Associations between term low birth weight and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Measured pollutant concentrations interpolated by empirical Bayesian kriging (EBK)				
$PM_{2.5}$	68,887	6.47	0.982 (0.956; 1.009)	0.20
O_3	68,952	10.80	1.035 (1.017; 1.054)	<0.01
NO_2	68,574	10.25	0.991 (0.960; 1.022)	0.56
UCD/CIT modeled concentrations at the 4 km × 4 km resolution, by fraction and species				
Primary $PM_{0.1}$	65,391	1.359	0.996 (0.981; 1.011)	0.58
OC in $PM_{0.1}$	65,391	0.958	0.995 (0.981; 1.009)	0.49
EC in $PM_{0.1}$	65,391	0.131	1.015 (0.994; 1.037)	0.16
SOA in $PM_{0.1}$	65,391	0.060	1.053 (1.020; 1.088)	<0.01
Primary $PM_{2.5}$	65,391	8.225	0.986 (0.968; 1.004)	0.13
OC in $PM_{2.5}$	65,391	3.630	0.986 (0.969; 1.004)	0.12
EC in $PM_{2.5}$	65,391	1.265	1.013 (0.991; 1.034)	0.24
SOA in $PM_{2.5}$	65,391	0.228	1.025 (0.999; 1.051)	0.06
Ammonium in $PM_{2.5}$	65,391	1.189	1.019 (0.993; 1.046)	0.16
Nitrates in $PM_{2.5}$	65,391	2.916	1.025 (0.998; 1.053)	0.07
Sulfates in $PM_{2.5}$	65,391	0.535	0.998 (0.986; 1.009)	0.69
UCD_P modeled concentrations at the 4 km × 4 km resolution, by species, in $PM_{2.5}$				
K in $PM_{2.5}$	48,541	0.053	No convergence	NA
Cr in $PM_{2.5}$	48,541	0.002	0.995 (0.988; 1.003)	0.20
Fe in $PM_{2.5}$	48,541	0.191	No convergence	NA
Ti in $PM_{2.5}$	48,541	0.008	0.991 (0.974; 1.009)	0.34
Mn in $PM_{2.5}$	48,541	0.004	1.001 (0.985; 1.017)	0.91
Sr in $PM_{2.5}$	48,541	0.001	0.991 (0.970; 1.012)	0.38
As in $PM_{2.5}$	48,541	0.001	1.000 (0.996; 1.004)	0.97
Ca in $PM_{2.5}$	48,541	0.048	0.994 (0.973; 1.015)	0.56
Zn in $PM_{2.5}$	48,541	0.002	0.997 (0.985; 1.008)	0.58
UCD_P modeled concentrations at the 4 km × 4 km resolution, by fraction and source				
Onroad gasoline $PM_{0.1}$	48,541	0.083	1.051 (1.015; 1.089)	0.01
Onroad diesel $PM_{0.1}$	48,541	0.070	1.030 (1.000; 1.060)	0.05
Commercial meat cooking $PM_{0.1}$	48,541	0.124	1.032 (1.008; 1.056)	0.01
Wood burning $PM_{0.1}$	48,541	0.260	0.986 (0.974; 0.999)	0.03
Onroad gasoline $PM_{2.5}$	48,541	0.385	1.045 (1.011; 1.079)	0.01
Onroad diesel $PM_{2.5}$	48,541	0.397	1.024 (0.999; 1.049)	0.06
Commercial meat cooking $PM_{2.5}$	48,541	1.094	1.011 (0.990; 1.032)	0.32
Wood burning $PM_{2.5}$	48,541	1.736	0.982 (0.968; 0.996)	0.01

Table continues next page

Note: $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; $PM_{0.1}$ = particulate matter ≤0.1 μm in aerodynamic diameter (ultrafine particles); As = arsenic; Ca = calcium; CO = carbon monoxide; Cr = chromium; EC = elemental carbon; Fe = iron; K = potassium; Mn = manganese; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; O_3 = ozone; OC = organic carbon; PAH = polycyclic aromatic hydrocarbon; SOA = secondary organic aerosols; Sr = strontium; Ti = titanium; UFPs = ultrafine particles; Zn = zinc.

[a] Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b] IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c] For estimated pollutant concentration, odds ratios are expressed per IQR.

Table 5 (*Continued*). Associations between term low birth weight and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Spatial (PAH) or spatiotemporal (NO_2) regression models (in Los Angeles County only)				
PAH	21,921	6.54	0.995 (0.971; 1.02)	0.69
NO_2	21,921		No convergence	
CALINE4 modeled concentrations				
UFP number	66,120	6444	1.001 (0.989; 1.014)	0.85
CO	66,120	60.63	0.999 (0.985; 1.012)	0.83
NO_x	66,120	6.10	1.003 (0.991; 1.015)	0.62
Traffic density (odds ratios per 10,000 vehicles per day per meter, within buffers of different sizes)				
50 m buffer	69,575		1.124 (1.040; 1.214)	<0.01
150 m buffer	69,575		1.006 (0.967; 1.046)	0.77
250 m buffer	69,575		0.994 (0.960; 1.029)	0.73
350 m buffer	69,575		1.009 (0.974; 1.046)	0.61
Road length (odds ratios per 100 m of road length, within buffers of different sizes)				
50 m buffer	69,575		1.037 (1.020; 1.054)	<0.01
150 m buffer	69,575		1.004 (1.001; 1.007)	0.02
250 m buffer	69,575		1.001 (1.000; 1.003)	0.08
350 m buffer	69,575		1.001 (1.000; 1.002)	0.05
Distance to roadways				
Less than 50 m	70,003		1.044 (1.022; 1.068)	<0.01
Less than 100 m	70,003		1.023 (1.004; 1.042)	0.02
Less than 150 m	70,003		1.008 (0.990; 1.027)	0.37
Less than 200 m	70,003		1.007 (0.988; 1.026)	0.47
Less than 250 m	70,003		1.006 (0.985; 1.027)	0.58
Less than 300 m	70,003		1.013 (0.989; 1.037)	0.29

Note: $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; $PM_{0.1}$ = particulate matter ≤0.1 μm in aerodynamic diameter (ultrafine particles); As = arsenic; Ca = calcium; CO = carbon monoxide; Cr = chromium; EC = elemental carbon; Fe = iron; K = potassium; Mn = manganese; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; O_3 = ozone; OC = organic carbon; PAH = polycyclic aromatic hydrocarbon; SOA = secondary organic aerosols; Sr = strontium; Ti = titanium; UFPs = ultrafine particles; Zn = zinc.

[a] Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b] IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c] For estimated pollutant concentration, odds ratios are expressed per IQR.

In addition, term LBW risk was significantly increased in women living within 50 m (OR: 1.044; 95% CI: 1.022–1.068) and 100 m (OR: 1.023; 95% CI: 1.004–1.042) of a roadway. Odds ratios regularly decreased from 50 m to 250 m, although none was statistically significant beyond 100 m (Table 5).

We explored the association between term LBW and exposure to air pollution during different trimesters of pregnancy for the air pollution indicators measured and modeled with sufficient temporal resolution (e.g., not the road traffic indicators or the Los Angeles–specific NO_2 and PAH models). Associations between either measured or modeled pollutant concentrations appear to be consistently stronger for exposure occurring during the third trimester of pregnancy than during the first two, except for O_3 and SOA (the association being strongest for the second trimester of pregnancy) (Appendix B, Table B.2). Term LBW was positively associated with exposure to EC, ammonium, and nitrates averaged on the third trimester of pregnancy, but not during other temporal windows of exposure.

When associations between term LBW and exposure averaged on the entire pregnancy were examined in

specific subgroups, overall associations with primary emissions appeared stronger in the group with the lowest education level (less than 8th grade), although significant heterogeneity of risk across education subgroups was observed only for EC in $PM_{2.5}$, onroad gasoline, and meat cooking, and the number of cases in the group with the lowest education level was small (Appendix B, Table B.3). However, when indices of traffic density, road length, or residential distance to roadways were considered, associations were higher in the group with some college education. This interaction was statistically significant in the 50 m and 150 m buffers.

When the population was stratified according to quartiles of median income at the census block-group level, the highest associations were generally observed in either the first or the fourth quartiles of median income (Appendix B, Table B.4). This pattern was consistent across most exposure indicators. However, heterogeneity tests could not be conducted for many air pollutants, because of convergence problems in many subgroups.

The comparison of the magnitude of associations across race/ethnicities was even more difficult for ambient pollutant concentrations because very few models converged in the smallest subgroup of African American mothers (Appendix B, Table B.5). More models converged for traffic density, road length, and residential distance to roadways. No significant heterogeneity of risk across race/ethnicity subgroups was observed for any air pollution indicator.

Associations between air pollutant concentrations (either measured or modeled) were generally higher in mothers with chronic hypertension than without this condition, although interactions were significant only for NO_2 and ammonium and close to significant for O_3 (Appendix B, Table B.6). Odds ratios were generally slightly higher in mothers with diabetes than without it (Appendix B Table, B.7), but no significant heterogeneity of associations was detected for this condition. Again, many models did not converge.

We observed no significant heterogeneity of associations or consistent pattern for BMI at the beginning of pregnancy (Appendix B, Table B.8) or for weight gain during pregnancy (Appendix B, Table B.9). Lower associations between pollutant concentrations and term LBW were generally reported in mothers who declared smoking at some point during pregnancy than in mothers who did not (Appendix B, Table B.10). This was significant for total $PM_{2.5}$, UFP from traffic sources modeled with CALINE4, and distance to roadways (the < 300 m category). However, because the number of mothers who declared that they smoked was very small, the estimates in this subgroup were unstable.

PRETERM BIRTHS

For exposure averaged on the entire pregnancy, PTB risk was positively associated with EBK-interpolated measurements of total $PM_{2.5}$, O_3, and NO_2 (Table 6). The largest association was observed for total $PM_{2.5}$ (interquartile OR: 1.172; 95% CI: 1.158–1.187).

Associations between PTB and primary $PM_{2.5}$ (interquartile OR: 1.045; 95% CI: 1.037–1.053) and $PM_{0.1}$ (interquartile OR: 1.038; 95% CI: 1.009–1.068) modeled at a 4 km × 4 km resolution were weaker than for total $PM_{2.5}$ but still statistically significant. For sources of primary $PM_{0.1}$, the strongest associations were observed for onroad gasoline (interquartile OR: 1.096; 95% CI: 1.080–1.112), followed by onroad diesel (interquartile OR: 1.068; 95% CI: 1.055–1.081), and commercial meat cooking (interquartile OR: 1.058; 95% CI: 1.047–1.069), and only a slight positive association was observed for wood burning (interquartile OR:1.009; 95% CI: 1.002–1.016). Patterns by source were similar for primary $PM_{2.5}$, but overall, associations appear slightly weaker than for $PM_{0.1}$.

For $PM_{2.5}$ composition modeled at a 4 km × 4 km resolution, the strongest positive associations with PTB risk were observed for nitrate, ammonium, and SOA, followed by EC, OC, and potassium (K). Slight decreases in risk were associated with calcium (Ca) and strontium (Sr) exposure. No significant positive association was observed for the other chemical species investigated.

No association was observed between PTB and spatially modeled PAH (in Los Angeles County only). NO_2 was inversely associated with PTB in this setting.

When primary traffic emissions modeled at fine geographical resolution using CALINE4 were considered, only a slight positive association was observed between PTB and NO_x in the entire population (OR per IQR in exposure: 1.007; 95% CI: 1.002–1.013) (Table 6). However, when analyses were restricted to the population in which maternal addresses could be geocoded most accurately (i.e., at the exact parcel centroid), UFP number was slightly but significantly associated with PTB (OR per IQR in exposure: 1.015; 95% CI: 1.000–1.031), whereas the association with NO_x had the same magnitude as in the entire population but became insignificant (Appendix C [available on the HEI Web site], Table C.1). With "medium geocoding accuracy," that is, matching within 50 m of a parcel (leaving about half the population for analyses), positive and significant associations were observed for all three pollutants ($PM_{0.1}$, CO, and NO_x).

Only negative or nonsignificant associations were observed between PTB and traffic density, road length, or distance to roads in the entire population (Table 6).

Table 6. Associations between preterm births and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Measured pollutant concentrations interpolated by empirical Bayesian kriging (EBK)				
$PM_{2.5}$	377,631	6.51	1.172 (1.158; 1.187)	<0.01
O_3	379,274	11.69	1.087 (1.075; 1.098)	<0.01
NO_2	376,995	10.11	1.107 (1.093; 1.121)	<0.01
UCD/CIT modeled concentrations at the 4 km × 4 km resolution, by fraction and species				
Primary $PM_{0.1}$	356,078	1.389	1.038 (1.009; 1.068)	<0.01
OC in $PM_{0.1}$	356,078	0.984	1.032 (1.025; 1.038)	<0.01
EC in $PM_{0.1}$	356,078	0.131	1.050 (1.043; 1.058)	<0.01
SOA in $PM_{0.1}$	356,078	0.061	1.131 (1.119; 1.144)	<0.01
Primary $PM_{2.5}$	356,078	8.358	1.045 (1.037; 1.053)	<0.01
OC in $PM_{2.5}$	356,078	3.718	1.033 (1.026; 1.040)	<0.01
EC in $PM_{2.5}$	356,078	1.260	1.045 (1.038; 1.053)	<0.01
SOA in $PM_{2.5}$	356,078	0.243	1.101 (1.089; 1.114)	<0.01
Ammonium in $PM_{2.5}$	356,078	1.194	1.152 (1.140; 1.164)	<0.01
Nitrates in $PM_{2.5}$	356,078	2.900	1.157 (1.145; 1.168)	<0.01
Sulfates in $PM_{2.5}$	356,078	0.502	1.001 (0.998; 1.005)	0.52
UCD_P modeled concentrations at the 4 km × 4 km resolution, by species, in $PM_{2.5}$				
K in $PM_{2.5}$	261,653	0.053	1.038 (1.028; 1.048)	<0.01
Cr in $PM_{2.5}$	261,653	0.002	0.999 (0.996; 1.002)	0.46
Fe in $PM_{2.5}$	261,653	0.191	0.996 (0.983; 1.010)	0.58
Ti in $PM_{2.5}$	261,653	0.008	1.001 (0.992; 1.010)	0.79
Mn in $PM_{2.5}$	261,653	0.004	1.005 (0.998; 1.012)	0.18
Sr in $PM_{2.5}$	261,653	0.001	0.985 (0.975; 0.995)	<0.01
As in $PM_{2.5}$	261,653	0.001	0.999 (0.998; 1.000)	0.14
Ca in $PM_{2.5}$	261,653	0.048	0.976 (0.966; 0.986)	<0.01
Zn in $PM_{2.5}$	261,653	0.002	1.001 (0.998; 1.005)	0.39
UCD_P modeled concentrations at the 4 km × 4 km resolution, by fraction and source				
Onroad gasoline $PM_{0.1}$	261,653	0.083	1.096 (1.080; 1.112)	<0.01
Onroad diesel $PM_{0.1}$	261,653	0.070	1.068 (1.055; 1.081)	<0.01
Commercial meat cooking $PM_{0.1}$	261,653	0.124	1.058 (1.047; 1.069)	<0.01
Wood burning $PM_{0.1}$	261,653	0.269	1.009 (1.002; 1.016)	0.02
Onroad gasoline $PM_{2.5}$	261,653	0.387	1.083 (1.068; 1.097)	<0.01
Onroad diesel $PM_{2.5}$	261,653	0.110	1.051 (1.038; 1.064)	<0.01
Commercial meat cooking $PM_{2.5}$	261,653	1.090	1.033 (1.024; 1.042)	<0.01
Wood burning $PM_{2.5}$	261,653	1.802	1.017 (1.009; 1.026)	<0.01

Table continues next page

[a]Cases and controls were matched on the year of conception. Odds ratios were estimated using conditional logistic regression models, adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using polynomial functions.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration, odds ratios are expressed per IQR.

Table 6 (*Continued*). Associations between preterm births and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Spatial (PAH) or spatiotemporal (NO_2) regression models (in Los Angeles County only)				
PAH	114,173	6.49	0.995 (0.987; 1.004)	0.30
NO_2	114,173	10.83	0.565 (0.535; 0.596)	<0.01
CALINE4 modeled concentrations				
UFP number	352,327	6460	0.995 (0.989; 1.000)	0.07
CO	352,327	60.10	1.002 (0.996; 1.008)	0.52
NO_x	352,327	6.06	1.007 (1.002; 1.013)	0.01
Traffic density (odds ratios per 10,000 vehicles per day per meter, within buffers of different sizes)				
50 m buffer	380,951		0.998 (0.995; 1.001)	0.11
150 m buffer	380,951		1.000 (0.998; 1.001)	0.79
250 m buffer	380,951		0.997 (0.996; 0.999)	<0.01
350 m buffer	380,951		0.997 (0.995; 0.998)	<0.01
Road length (odds ratios per 100 m of road length, within buffers of different sizes)				
50 m buffer	380,951		0.993 (0.986; 0.999)	0.02
150 m buffer	380,951		0.999 (0.998; 1.000)	0.13
250 m buffer	380,951		0.999 (0.998; 0.999)	0.00
350 m buffer	380,951		0.999 (0.999; 0.999)	0.00
Distance to roadways				
Less than 50 m	381,052		0.992 (0.984; 1.000)	0.04
Less than 100 m	381,052		0.999 (0.992; 1.007)	0.89
Less than 150 m	381,052		0.991 (0.984; 0.999)	0.02
Less than 200 m	381,052		0.981 (0.973; 0.989)	0.00
Less than 250 m	381,052		0.976 (0.966; 0.985)	0.00
Less than 300 m	381,052		0.974 (0.963; 0.984)	0.00

[a]Cases and controls were matched on the year of conception. Odds ratios were estimated using conditional logistic regression models, adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using polynomial functions.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration, odds ratios are expressed per IQR.

However, for subgroups with better geocoding accuracy, the road traffic indicators had some positive associations with PTB (Appendix C, Table C.2). In the subgroup with medium geocoding accuracy, PTB was positively associated with traffic density in the 50 and 150 m buffers, with road length in the 150 m buffer, and with living within 100 m or 150 m of a roadway. In the small subgroup geocoded at the exact parcel centroid, positive associations with traffic density and distance to roads were observed in even smaller buffers (50 m). Living within 100 or 50 m of a roadway was also associated with an increased PTB risk (Appendix C, Table C.2).

We explored the association between PTB and some air pollution indicators during different time windows: the first month, the first trimester, and the last month of pregnancy. The ORs were higher for exposure averaged over the entire pregnancy (Table 6) than for exposure considered during any of these time windows (Appendix C, Table C.3).

When associations between PTB and exposure averaged on the entire pregnancy were observed in specific subgroups, associations with air pollutant concentrations were typically stronger as the level of maternal education decreased (Appendix C, Table C.4). This pattern was

observed—although it was often not statistically significant—for all pollutants except for secondary pollutants (O_3, ammonium, nitrates, and sulfates); NO_2 using kriging; PM from wood burning; and NO_x modeled using CALINE4. No such pattern was observed for traffic density, road length, or residential distance to roadways. In both the $PM_{0.1}$ and the $PM_{2.5}$ fractions, interactions were significant for total primary particle mass, OC, and EC, and for primary particle mass from each source. (Although no clear pattern was observed for wood burning, the highest association was observed in mothers with intermediate educational level, that is, from 9th grade to high school.)

When the population was stratified according to quartiles of median income at the census block-group level, the strongest associations between PTB and pollutant concentrations (either modeled or measured) were generally observed in the two lower quartiles of median income rather than in the two upper ones (Appendix C, Table C.5). Interactions by income were significant in both the $PM_{0.1}$ and the $PM_{2.5}$ fractions, for total primary particle mass, OC, and EC and for primary particle mass from each source, but also for nitrates and sulfates in the $PM_{2.5}$ fraction. No significant interaction by income was observed for traffic density, road length, or residential distance to roadways.

Comparison across race/ethnicities showed that the associations between PTB and air pollutant concentrations (either measured or modeled) were generally higher in African American and Hispanic mothers than in white non-Hispanic or Asian mothers (Appendix C, Table C.6). Interactions were significant or close to significance for all air pollutant variables, except for nitrates in $PM_{2.5}$ and PM from wood burning. However, associations between PTB and traffic density, road length, and residential distance to roadways were always highest in white non-Hispanic mothers and lowest in Asian mothers. Interactions by race/ethnicity were also significant for these traffic indicators.

In mothers with chronic hypertension, associations between PTB and NO_2 interpolated with EBK, for primary PM from gasoline, meat cooking, and NO_x from traffic modeled using CALINE4 were significantly higher than in those without chronic hypertension (Appendix C, Table C.7). Stronger positive associations in mothers with chronic hypertension than those without this condition were also observed for traffic density, road length, and distance to roads, but this association was significant only for distance to roads. However, a statistically significant, opposite pattern was observed for ammonium and primary PM from wood burning.

Associations between air pollution indicators (measured or modeled concentrations, traffic density, road length, and distance to roads) were generally higher in mothers without diabetes than those with this condition (Appendix C, Table C.8). In both the $PM_{0.1}$ and the $PM_{2.5}$ fractions, interactions were significant for total primary particle mass, OC, and EC and for primary particle mass from meat cooking. The interactions were also significant for measured total $PM_{2.5}$ interpolated with EBK and for ammonium and nitrates in this size fraction.

Analyses by subgroups of BMI at the beginning of pregnancy overall suggest that the higher the BMI, the greater the association between PTB and the concentrations of primary pollutants (Appendix C, Table C.9). The only exception to this trend was in mothers with BMI ≥ 35 at the beginning of pregnancy; this was the smallest subgroup. A similar pattern was also observed for OC in $PM_{2.5}$. In both the $PM_{0.1}$ and the $PM_{2.5}$ fractions, the interactions were statistically significant for NO_2, total primary particle mass, EC, and OC. An inverse pattern was observed with some secondary pollutants (O_3, nitrates, and ammonium). Interactions by BMI were also statistically significant for these pollutants. Significant interactions by BMI were also observed for CALINE4 predictions and simple traffic indices (traffic density, road length, and distance to roads), but the patterns of associations with BMI were less clear for these air pollution indicators.

Interactions by smoking were significant or nearly significant for only a few air pollutants: Associations were higher in smoking mothers for total $PM_{2.5}$ and ammonium in $PM_{2.5}$. However, opposite patterns were observed for O_3, CALINE4 predictions, and some road indicators (Appendix C, Table C.10). As described for LBW, only a small number of mothers with PTB infants declared that they smoked. These small numbers might have resulted in an unstable estimate in this subgroup.

PREECLAMPSIA

For exposure averaged on the entire pregnancy, preeclampsia risk was negatively associated with EBK-interpolated measurements of O_3 (interquartile OR: 0.92; 95% CI 0.869–0.974) (Table 7) but not associated with NO_2 or total $PM_{2.5}$.

There was no association with primary $PM_{2.5}$ or $PM_{0.1}$ modeled at a 4 km × 4 km resolution. For $PM_{2.5}$ composition, preeclampsia was positively associated with K but negatively with sulfates. Preeclampsia was also negatively associated with EC in both the $PM_{2.5}$ and the $PM_{0.1}$ fractions. There was no association with PM from various sources modeled at a 4 km × 4 km resolution, except a positive association with $PM_{2.5}$ from wood burning.

A positive and nearly significant association was observed between preeclampsia and PAH estimated by

spatiotemporal regression (in Los Angeles County only). However, in the same setting, NO_2 was inversely associated with preeclampsia.

When we modeled primary traffic emissions at a finer geographical resolution using CALINE4, we found a negative association between preeclampsia and UFPs in the entire population. A significant inverse association was also observed for CO in the subgroup of the population with medium geocoding accuracy (either exact or approximate geocoding to parcel level, which left about half the population for analyses). However, with the most accurate level of geocoding (geocoding at the exact parcel centroid), the significant association disappeared (but the sample size was small) (Appendix D, Table D.1).

The association between preeclampsia and traffic density was more complex (Table 7 and Appendix D, Table D.2). In the entire population, traffic density was not associated with preeclampsia. In the subset with medium geocoding accuracy, associations were generally positive and strongest in the 50 m buffer. However, a significant positive association was only observed in the 50 m buffer in the subset. In the subset with the best geocoding accuracy (at the exact parcel centroid), there were significant positive associations in the 150, 250, and 350 m buffers, but there was no increase in the magnitude of associations from larger to smaller buffers. Associations between preeclampsia and road length in the total population revealed no consistent pattern. Analyses in the subset with the best geocoding accuracy suggested a sharp increase in risk in the 50 m buffer, but the related OR did not reach statistical significance, because of the small sample size. Analyses on residential proximity to roadways in the entire population showed no consistent pattern either.

We explored the association between preeclampsia and exposure to some air pollution indicators during different time windows, and no consistent pattern was observed (Appendix D, Table D.3). For example, when exposure during the first trimester of pregnancy was examined, preeclampsia was negatively associated with NO_2 (either interpolated with EBK or based on the spatiotemporal regression model in Los Angeles County) and to primary particles from all sources but not with secondary species in particles (ammonium, nitrates, or sulfates). There was no significant association with total $PM_{2.5}$ measurements interpolated with EBK during the first trimester. Exposure to ozone and SOA (in either the $PM_{2.5}$ or the $PM_{0.1}$ fraction) during the first trimester was associated with an increased preeclampsia risk, whereas no negative associations were documented in the whole population.

Preeclampsia was inversely associated with ozone during the second and third trimesters of pregnancy, and with SOA during the third trimester. Preeclampsia was positively associated with ammonium and nitrate, but negatively with sulfates, during the second trimester of pregnancy. A positive association between preeclampsia and PM from wood burning during the third trimester of pregnancy was observed. Still, during the second and third trimesters of pregnancy, preeclampsia was negatively associated with NO_2 estimated using a spatiotemporal regression model in Los Angeles County and with UFP number also during the third trimester from traffic modeled at fine resolution using CALINE4.

The subgroup analyses revealed few consistent patterns, and many models did not converge. Odds ratios were < 1 in most subgroups and tended to be even lower in the subgroups with the lowest education (Appendix D, Table D.4) and the lowest income (Appendix D, Table D.5), but the interactions were not statistically significant. There was no consistent pattern according to race/ethnicity (Appendix D, Table D.6), although significant interactions were detected for some pollutants, and ORs were even lower in Asians and non-Hispanic whites than in African Americans or Hispanics. Significant interactions by BMI were observed only for distance to roads, but no consistent patterns across categories were observed (Appendix D, Table D.7).

GESTATIONAL DIABETES MELLITUS

Note that GDM data were available only for 3 years of the 8-year study period. When exposures were averaged on the entire pregnancy, GDM was negatively associated with NO_2 measurements (but not O_3 or total $PM_{2.5}$) interpolated with EBK (Table 8). GDM was also negatively associated with $PM_{2.5}$ and $PM_{0.1}$ modeled at the 4 km × 4 km resolution, whatever the sources and chemical species considered, except for three chemical species (manganese [Mn], arsenic [As], and Ca), for which no significant negative association was observed.

No association was observed between PAH estimated by spatially modeled PAH (in Los Angeles County only) and GDM. However, NO_2 was positively associated with GDM. No significant association between GDM and CALINE4 estimates of primary traffic emissions was observed, although an inverse association with NO_x is close to statistical significance.

Associations between GDM and traffic density were generally positive but not statistically significant, and were strongest in the 250 m buffer. No statistically significant associations were reported in the subgroups with medium and best geocoding accuracy (results not shown).

For road length, a positive (but, again, not significant) association was reported for the 50 m buffer, and no

Table 7. Associations between preeclampsia and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Measured pollutant concentrations interpolated by empirical Bayesian kriging (EBK)				
$PM_{2.5}$	74,011	6.49	1.002 (0.896; 1.120)	0.97
O_3	73,914	10.94	0.920 (0.869; 0.974)	<0.01
NO_2	73,113	10.19	0.940 (0.820; 1.078)	0.38
UCD/CIT modeled concentrations at the 4 km × 4 km resolution, by fraction and species				
Primary $PM_{0.1}$	68,551	1.366	0.970 (0.936; 1.004)	0.08
OC in $PM_{0.1}$	68,551	0.966	0.974 (0.942; 1.007)	0.12
EC in $PM_{0.1}$	68,551	0.131	0.935 (0.889; 0.983)	0.01
SOA in $PM_{0.1}$	68,551	0.060	0.982 (0.901; 1.070)	0.68
Primary $PM_{2.5}$	68,551	8.303	0.976 (0.936; 1.018)	0.26
OC in $PM_{2.5}$	68,551	3.664	0.984 (0.949; 1.021)	0.40
EC in $PM_{2.5}$	68,551	1.259	0.932 (0.884; 0.982)	0.01
SOA in $PM_{2.5}$	68,551	0.229	0.986 (0.927; 1.049)	0.66
Ammonium in $PM_{2.5}$	68,551	1.193	1.061 (0.993; 1.135)	0.08
Nitrates in $PM_{2.5}$	68,551	2.927	1.039 (0.974; 1.109)	0.25
Sulfates in $PM_{2.5}$	68,551	0.530	0.940 (0.895; 0.988)	0.01
UCD_P modeled concentrations at the 4 km × 4 km resolution, by species, in $PM_{2.5}$				
K in $PM_{2.5}$	51,058	0.053	1.069 (1.025; 1.115)	<0.01
Cr in $PM_{2.5}$	51,058	0.002	0.998 (0.991; 1.004)	0.48
Fe in $PM_{2.5}$	51,058	0.191	1.046 (0.993; 1.101)	0.09
Ti in $PM_{2.5}$	51,058	0.008	1.001 (0.982; 1.020)	0.93
Mn in $PM_{2.5}$	51,058	0.004	No convergence	NA
Sr in $PM_{2.5}$	51,058	0.001	No convergence	NA
As in $PM_{2.5}$	51,058	0.001	1.001 (0.998; 1.004)	0.61
Ca in $PM_{2.5}$	51,058	0.048	No convergence	NA
Zn in $PM_{2.5}$	51,058	0.002	1.000 (0.991; 1.009)	1.00
UCD_P modeled concentrations at the 4 km × 4 km resolution, by fraction and source				
Onroad gasoline $PM_{0.1}$	51,058	0.082	0.944 (0.874; 1.020)	0.15
Onroad diesel $PM_{0.1}$	51,058	0.070	No convergence	NA
Commercial meat cooking $PM_{0.1}$	51,058	0.123	0.969 (0.922; 1.017)	0.20
Wood burning $PM_{0.1}$	51,058	0.264	1.020 (0.995; 1.045)	0.11
Onroad gasoline $PM_{2.5}$	51,058	0.383	0.964 (0.901; 1.030)	0.27
Onroad diesel $PM_{2.5}$	51,058	0.398	1.011 (0.954; 1.072)	0.70
Commercial meat cooking $PM_{2.5}$	51,058	1.090	0.989 (0.954; 1.026)	0.56
Wood burning $PM_{2.5}$	51,058	1.759	1.035 (1.005; 1.065)	0.02

Table continues next page

[a]Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration, odds ratios are expressed per IQR.

Table 7 (*Continued*). Associations between preeclampsia and air pollution in California, 2001–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Spatial (PAH) or spatiotemporal (NO_2) regression models (in Los Angeles County only)				
PAH	17,675	6.53	1.033 (0.997; 1.071)	0.07
NO_2	17,675	11.07	0.904 (0.850; 0.961)	<0.01
CALINE4 modeled concentrations				
UFP number	71,522	6372	0.979 (0.968; 0.990)	<0.01
CO	71,522	60.28	0.971 (0.938; 1.006)	0.11
NO_x	71,522	6.05	0.983 (0.957; 1.010)	0.22
Traffic density (odds ratios per 10,000 vehicles per day per meter, within buffers of different sizes)				
50 m buffer	75,196		1.005 (0.934; 1.081)	0.89
150 m buffer	75,196		1.006 (0.966; 1.048)	0.76
250 m buffer	75,196		1.005 (0.966; 1.046)	0.80
350 m buffer	75,196		1.000 (0.958; 1.043)	0.99
Road length (odds ratios per 100 m of road length, within buffers of different sizes)				
50 m buffer	75,196		0.998 (0.984; 1.013)	0.83
150 m buffer	75,196		1.000 (0.997; 1.003)	0.89
250 m buffer	75,196		0.999 (0.998; 1.001)	0.54
350 m buffer	75,196		1.000 (0.999; 1.001)	0.46
Distance to roadways				
Less than 50 m	79,597		0.987 (0.965; 1.009)	0.23
Less than 100 m	79,597		1.005 (0.986; 1.024)	0.62
Less than 150 m	79,597		1.017 (0.998; 1.037)	0.08
Less than 200 m	79,597		1.002 (0.983; 1.022)	0.81
Less than 250 m	79,597		0.992 (0.971; 1.014)	0.48
Less than 300 m	79,597		1.003 (0.979; 1.027)	0.82

[a]Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration, odds ratios are expressed per IQR.

associations were found in the larger buffer sizes. Associations that were not statistically significant were reported in the subgroups with medium and best geocoding accuracy, and no convergence was reached in the 50 m buffer model (results not shown).

Residential proximity to roadways in the entire population showed no consistent pattern. Convergence was usually not reached in subgroups with medium and best geocoding accuracy, probably due to the rarity of observations (e.g., living within 50 or 100 m of a road), because our analyses for GDM were based on 2006–2008 birth records, whereas we used 2001–2008 for other pregnancy outcomes.

We examined the association between GDM and exposure to some air pollution indicators during different time windows (Appendix E, Table E.1). GDM was positively associated with O_3 exposure during the first trimester of pregnancy. However, GDM was inversely associated with primary PM exposures that occurred during each of the three trimesters of pregnancy. This was also the case for sulfates, but it was not significant for nitrates or ammonium. GDM was also inversely associated with total $PM_{2.5}$

interpolated with EBK during the third trimester of pregnancy. GDM was inversely associated with NO_2 measurements interpolated with EBK during the first two trimesters of pregnancy, but was positively associated with NO_2 estimated using the spatiotemporal regression model in Los Angeles County during the same periods. GDM was inversely associated with NO_x exposure estimated using CALINE 4 during the first trimester of pregnancy.

The subgroup analyses revealed few consistent patterns (Appendix E, Table E.3–E.6). Odds ratios were < 1 in most subgroups, and ORs tended to be even lower in the subgroups with the lowest education or the lowest income, but not for traffic density and income.

DISCUSSION AND CONCLUSIONS

SUMMARY OF THE MAIN FINDINGS

This study had a very large sample size and was built on a wealth of complementary matrices of air pollution exposure estimates. Our main finding is that both PTB and term LBW (a marker for intrauterine growth restriction) are associated with some primary and secondary components of air pollution. Both outcomes are positively associated with primary PM emitted by traffic, which is in general agreement with previous research. These pregnancy outcomes are also associated with PM from commercial meat cooking, an air pollution source that has been less studied so far. Associations were slightly stronger with $PM_{0.1}$ than with $PM_{2.5}$ from these sources. PTB is also associated with EBK-interpolated measurements of NO_2, with EC, and, though more weakly, with PM from wood burning. Exposure to EC during the last trimester of pregnancy was also positively associated with term LBW.

Regarding secondary pollutants, O_3 was positively associated with both term LBW and PTB. This was also the case for SOA. Nitrates and ammonium were positively associated with PTB and with term LBW (but only for exposure averaged on the last trimester of pregnancy for term LBW). OC was positively associated with PTB but not term LBW. No association was observed between sulfates and PTB or term LBW. However, model performances need to be improved for this pollutant.

For total (measured) $PM_{2.5}$, which include both primary and secondary pollutants, a positive association was observed for PTB but not for term LBW.

We identified several population subgroups in which the associations between primary pollutants and birth outcomes were stronger. For both PTB and term LBW, the associations were stronger for mothers with low educational level or chronic hypertension. For PTB, the associations were stronger for mothers living in poorer neighborhoods; for African Americans or Hispanics; or for women having a higher BMI at the beginning of pregnancy.

We investigated the quality of reporting of preeclampsia and diabetes on a subset for which both birth certificate data and hospital-based birth records were available and found substantial underreporting for these conditions, with higher rates of underreporting in more socioeconomically deprived populations. The disparity suggests that the information available in birth certificates on maternal conditions such as preeclampsia or GDM is probably not appropriate to study the effects of air pollution on these conditions. Underreporting might explain the many negative associations we observed between air pollution indicators and either preeclampsia or GDM.

Air Pollution Indicators

All the air pollution indicators included in this study have respective strengths and limitations that need to be weighed in light of the purpose of the analysis. The EBK approach we used to interpolate measured pollutant concentrations allows retaining both their temporal and their spatial variability. However, because EBK includes no geographical covariates, it only models the general trends in spatial variations and lacks the level of detail needed to capture small-scale variations of air pollution. For this reason, we only applied EBK to pollutants that exhibit strong regional trends ($PM_{2.5}$, O_3, and NO_2). In addition, because the model relies solely on ambient monitoring station data, higher uncertainties in the estimates are expected in areas with sparse measurements (e.g., rural or suburban areas). Sensitivity analyses showed that weighting the EBK outputs inversely by the standard error of estimates did not markedly change the point estimates of the association but slightly narrowed the confidence intervals (data not shown). Further, because of computation constrains, only monthly mean concentrations have been used for spatial interpolation using EBK. The impact of using this coarse temporal resolution for the calculation of pregnancy and even trimester-specific mean concentrations was likely limited (Laurent et al. 2014), but it prevented us from studying the associations between pregnancy outcomes and air pollution exposure during narrow temporal windows (e.g., the first month or the last month of pregnancy).

Because the source-oriented chemical transport models have the advantage of modeling large areas, many species, different particle sizes, and various sources, we believe that these models are the most appropriate exposure assessment method for our current work; our main epidemiological results rely heavily on the estimates from

Table 8. Associations between gestational diabetes and air pollution in California, 2006–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Measured pollutant concentrations interpolated by empirical Bayesian kriging (EBK)				
$PM_{2.5}$	44,952	5.38	0.907 (0.814; 1.011)	0.08
O_3	44,949	9.96	0.988 (0.932; 1.048)	0.70
NO_2	44,772	8.77	0.822 (0.732; 0.923)	<0.01
UCD/CIT modeled concentrations at the 4 km × 4 km resolution, by fraction and species				
Primary $PM_{0.1}$	42,332	1.407	0.909 (0.862; 0.959)	<0.01
OC in $PM_{0.1}$	42,332	0.992	0.912 (0.868; 0.960)	<0.01
EC in $PM_{0.1}$	42,332	0.145	0.875 (0.820; 0.934)	<0.01
SOA in $PM_{0.1}$	42,332	0.058	0.965 (0.940; 0.990)	0.01
Primary $PM_{2.5}$	42,332	9.312	0.902 (0.840; 0.968)	<0.01
OC in $PM_{2.5}$	42,332	3.892	0.907 (0.854; 0.963)	<0.01
EC in $PM_{2.5}$	42,332	1.405	0.860 (0.805; 0.918)	<0.01
SOA in $PM_{2.5}$	42,332	0.260	0.868 (0.774; 0.974)	0.02
Ammonium in $PM_{2.5}$	42,332	1.243	0.869 (0.788; 0.959)	0.01
Nitrates in $PM_{2.5}$	42,332	2.930	0.896 (0.809; 0.994)	0.04
Sulfates in $PM_{2.5}$	42,332	0.555	0.946 (0.897; 0.996)	0.04
UCD_P modeled concentrations at the 4 km × 4 km resolution, by species, in $PM_{2.5}$				
K in $PM_{2.5}$	13,614	0.198	0.861 (0.79; 0.938)	<0.01
Cr in $PM_{2.5}$	13,614		No convergence	NA
Fe in $PM_{2.5}$	13,614		No convergence	NA
Ti in $PM_{2.5}$	13,614		No convergence	NA
Mn in $PM_{2.5}$	13,614	0.004	0.966 (0.932; 1.001)	0.06
Sr in $PM_{2.5}$	13,614	0.001	0.911 (0.865; 0.959)	<0.01
As in $PM_{2.5}$	13,614	0.001	0.994 (0.987; 1.001)	0.07
Ca in $PM_{2.5}$	13,614	0.051	0.960 (0.904; 1.019)	0.18
Zn in $PM_{2.5}$	13,614	0.002	0.973 (0.952; 0.996)	0.02
UCD_P modeled concentrations at the 4 km × 4 km resolution, by fraction and source				
Onroad gasoline $PM_{0.1}$	13,614	0.088	0.831 (0.743; 0.928)	<0.01
Onroad diesel $PM_{0.1}$	13,614	0.080	0.870 (0.795; 0.952)	<0.01
Commercial meat cooking $PM_{0.1}$	13,614	0.120	0.861 (0.791; 0.937)	<0.01
Wood burning $PM_{0.1}$	13,614	0.285	0.954 (0.915; 0.996)	0.03
Onroad gasoline $PM_{2.5}$	13,614	0.413	0.849 (0.769; 0.937)	<0.01
Onroad diesel $PM_{2.5}$	13,614	0.468	0.886 (0.822; 0.956)	<0.01
Commercial meat cooking $PM_{2.5}$	13,614	1.091	0.890 (0.833; 0.952)	<0.01
Wood burning $PM_{2.5}$	13,614	1.854	0.950 (0.908; 0.995)	0.03

Table continues next page

[a]Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration; odds ratios are expressed per IQR.

Table 8 (*Continued*). Associations between gestational diabetes and air pollution in California, 2006–2008[a]

Air pollution indicator	Cases	IQR[b]	Odds ratio (95% confidence interval)[c]	*P* value
Spatial (PAH) or spatiotemporal (NO_2) regression models (in Los Angeles County only)				
PAH	8913	6.57	1.007 (0.954; 1.063)	0.80
NO_2	8913	10.82	1.051 (1.015; 1.089)	0.01
CALINE4 modeled concentrations				
UFP number	42,203	6053	1.002 (0.984; 1.020)	0.85
CO	42,203	42.60	0.993 (0.971; 1.014)	0.50
NO_x	42,203	4.49	0.982 (0.964; 1.001)	0.06
Traffic density (odds ratios per 10,000 vehicles per day per meter, within buffers of different sizes)				
50 m buffer	45,483		0.994 (0.902; 1.097)	0.91
150 m buffer	45,483		1.001 (0.948; 1.057)	0.98
250 m buffer	45,483		1.025 (0.978; 1.075)	0.30
350 m buffer	45,483		1.006 (0.959; 1.054)	0.81
Road length (odds ratios per 100 m of road length, within buffers of different sizes)				
50 m buffer	45,483		1.017 (0.996; 1.037)	0.11
150 m buffer	45,483		1.001 (0.997; 1.006)	0.65
250 m buffer	45,483		1.000 (0.998; 1.002)	0.83
350 m buffer	45,483		1.000 (0.999; 1.001)	0.74
Distance to roadways				
Less than 50 m	45,486		0.999 (0.970; 1.029)	0.95
Less than 100 m	45,486		0.987 (0.962; 1.013)	0.33
Less than 150 m	45,486		0.986 (0.960; 1.012)	0.29
Less than 200 m	45,486		1.004 (0.979; 1.029)	0.77
Less than 250 m	45,486		1.007 (0.979; 1.037)	0.62
Less than 300 m	45,486		1.017 (0.984; 1.051)	0.31

[a]Odds ratios were estimated using generalized additive mixed models with random effects per hospital. Models were adjusted for race/ethnicity and educational level using categorical variables, and for maternal age and median household income at census block-group level using smoothing splines.

[b]IQR: interquartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements, and parts per billion for gaseous pollutants.

[c]For estimated pollutant concentration; odds ratios are expressed per IQR.

these models. Without the UCD_P and UCD/CIT models, we could not have predicted the spatiotemporal variations of the concentrations of chemical species in PM and the concentrations of primary PM from specific sources for two fractions ($PM_{2.5}$ and $PM_{0.1}$). Speciation monitors are scarce, and source apportionment studies are typically based on modeling instead of monitoring. Attributing ambient concentrations measured at a monitor site to populations living miles away can lead to bias, unless the purpose of the epidemiological investigation is purely to capture the temporal variations of background pollution levels (e.g., time-series studies) (Hu et al. 2015).

Any modeling process is bound to have uncertainties, but some validation studies have been conducted for UCD_P (Hu et al., 2014a,b) and UCD/CIT (Chen et al. 2010; Hu et al. 2015; Kleeman et al. 1997, 2007; Kleeman and Cass 2001; Mysliwiec and Kleeman 2002). We decided a priori to include in our analyses UCD_P estimates of primary PM from sources with satisfactory validation results. Onroad gasoline, diesel, commercial meat cooking, and wood burning matched these criteria (Hu et al. 2014b). They only represent a portion of the sources of PM potentially related to pregnancy outcomes, but are ubiquitous in the urban and rural environment. The

abundance of aerosols from commercial meat cooking has been confirmed in a number of receptor-oriented source-apportionment studies, in agreement with the current mechanistic source apportionment work (Ham and Kleeman 2011; Kleeman et al. 2009). For the commercial meat cooking, we included three emission subcategories: commercial—charbroiling; commercial—deep fat fry; and commercial—unspecified. These sources were generally located in areas with a high population density or along the highways or major surface streets. Wood burning included all sources that generate smoke from biomass combustion (Hu et al. 2015). This source was typically dominated by home-heating woodstoves and fireplaces during winter months, but it also included important sources such as agricultural burning and wildfires. Estimates of home-heating wood smoke emissions were based on county-wide estimates of firewood sales allocated spatially from census data describing home heating methods. Agricultural burning was estimated from seasonal-mean estimates spatially allocated by agricultural land-use types. Wildfires were estimated using satellite data as described in the Fire Inventory from National Center for Atmospheric Research (FINN) system. As more validations studies will be conducted and emission inventories enriched, it will be possible to study the influence of further validated sources in epidemiological studies of birth outcomes (Hu et al. 2014b).

We decided beforehand to include in the analyses only primary PM components for which correlations between monthly mean predictions and measured values were > 0.8 (we conducted correlation analysis only for $PM_{2.5}$ components, because measurement results for most components were available only for that fraction) (Hu et al. 2014b). For secondary species, we included pollutants with satisfactory model performance, as well as a few species with less-than-satisfactory model performance such as sulfates because of their important contribution to total PM mass (Bell et al. 2007).

The current UCD/CIT and UCD_P models are less desirable for estimating secondary PM (at least as of today), high-temporal-resolution data, and pollutants with high spatial heterogeneity at a small scale (e.g., UFPs) (Hu et al. 2015). Incomplete understanding of SOA formation mechanisms leads to OC bias in the results in summertime, although OC bias did not affect OC predictions in winter, when concentrations are typically highest. With the models' limited capability to estimate daily and weekly variations of pollutant concentrations, they cannot reliably estimate the acute effects of exposures (e.g., the impact of short-term air pollution exposure on preterm delivery). Temporal and spatial uncertainties were found for the mobile emissions generated by the EMFAC2007 model. In addition, the WRF model's tendency to overpredict wind speed during stagnation events led to underpredictions of high PM concentrations, usually in winter months. The WRF model also generally underpredicted relative humidity and hence particulate nitrate formation, especially during winter months. Further, for the current study, the UCD_P estimates were only available for 2000–2006. Therefore, we could not use those estimates in the sensitivity analyses that additionally corrected for maternal smoking and BMI, since the data were available only for the years 2007–2008.

The spatiotemporal model for NO_2 presumably captures both the spatial and the temporal variability and thus provides the highest quality of data on ambient NO_2 concentrations. But as a data-driven statistical model, it is substantially influenced by the range of input variables. Extreme values for the input variables might lead to unrealistically high or low estimates. Although extreme input values have been controlled in this work, we cannot completely avoid this problem. In addition, the spatiotemporal models are costly to develop because intensive air pollution measurements (both long-term and episodic sampling) and spatial covariates are required for model development. Because of the limited resources, the model was only developed for the Los Angeles area rather than the entire state of California.

Our PAH model was one of first spatial models to estimate gas-phase PAH concentrations. However, we observed no statistically significant associations between PAH exposure and the four pregnancy outcomes. This result is likely because we only had 36 to 39 PAH sampling sites (compared with approximately 240 sites for NO_2/NO_x) for model development in the large metropolitan Los Angeles area. Because of the small number of samples, the spatial PAH models had a relatively coarse spatial resolution and were probably unable to capture the real spatial heterogeneity of PAH distributions. Another major weakness is that the PAH estimates lacked temporal variability, which is important in pregnancy outcome analysis.

Compared with the NO_2/NO_x and PAH spatial models, the CALINE4 dispersion model is cost-effective and does not require pollutant measurements. The model aims to capture solely local traffic emissions; no other sources, including traffic emissions far away from a receptor, are considered. CALINE4 outputs have limited temporal variability, for two reasons. First, this simple Gaussian dispersion model does not consider complex atmospheric mechanisms on transport, deposition, chemical reaction, and gas–particle transfer. Second, model inputs have limited temporal resolution (e.g., annual mean traffic counts,

estimated mixing height by season and time of day). Hence, the CALINE4 model is not suitable to examine acute health effects of exposure. Further, the model estimates are substantially influenced by the quality of the model input variables with different levels of uncertainty. For instance, the roadway and traffic data available were rather limited, and, thus, our final traffic count data set was a combination of measurement and estimated values. Finally, meteorological data from the nearest station was assigned to each subject. However, wind is sensitive to local topography (e.g., hills), obstructions (e.g., buildings, trees, towers), or surface roughness. Thus, wind from the nearest station may not represent wind at a particular residence, say, in downtown Los Angeles with dense, tall buildings.

Our results suggest that the traffic indicators (traffic density, roadway length, and distance to road) are positively associated with term LBW and with PTB (the latter only when analyses are restricted to the subsets of births with good geocoding accuracy), but the effect is mostly apparent in a narrow influential zone of 50 m of a residence. Both primary traffic-related pollutants and traffic noise might contribute to explain such associations (Dadvand et al. 2014b; Dzhambov et al. 2014; Gehring et al. 2014; Ristovska et al. 2014). A recent meta-analysis of 29 studies showed that women exposed to high noise levels (in most of the studies, ≥ 80 dB) during pregnancy were at a significantly higher risk for having small-for-gestational-age newborns, gestational hypertension, and infants with congenital malformations, but the effect was not significant for preeclampsia and PTB (Dzhambov et al. 2014). Ristovska and colleagues (2014) published a systematic review that included nine epidemiological studies related to environmental noise exposure and reproductive outcomes; they concluded that there is some evidence of adverse associations with environmental noise, especially for LBW. A recent study based on nearly 70,000 administrative birth records in Vancouver, Canada, reported that residential noise exposure was negatively associated with term birth weight, and the results were not sensitive to adjustment for air pollution exposure (Gehring et al. 2014). However, a new study in Barcelona, Spain, based on more than 6000 subjects reported that the increased risk of term LBW associated with proximity to major roads was partly mediated by air pollution and heat exposures, but not by noise exposure (Dadvand et al. 2014b). Because we did not estimate noise exposure as part of the current study, we cannot separate the effect of traffic-related air pollution and noise. Further studies will be needed to distinguish the influence of traffic-related noise from that of air pollution exposure on pregnancy outcomes.

Birth Certificate Data

The use of birth certificate data has its strengths and limitations. On the one hand, using birth certificates for the entire state of California over a period of 8 years afforded a sample population of about 4 million births. The large sample size provided substantial statistical power for analyses, even if they had to be conducted in more restricted case-control subsets because of the computational challenges of analyzing such a large population for four pregnancy outcomes and numerous indicators of air pollution exposure.

On the other hand, the quality of the information recorded in birth certificates greatly depends on the variable considered. Because birth weight is an objective measure, any related error is presumably minimal. Information about major determinants of pregnancy outcomes (PTB, birth weight, preeclampsia, and GDM), such as maternal age, race/ethnicity, and educational level, are thought to be reasonably accurate. The value of the median income per census block group was estimated from the geocoding of maternal addresses and linkage with census data. It therefore constitutes an objective measure with limited potential for error. The gestational age was generally estimated on mothers' self-reporting of their last menstrual period before birth, a measure that may lead to misclassification because of poor recall, postconception bleeding, or menstrual irregularities (Pearl et al. 2007). To limit the impact of such misclassifications on our analyses, we cleaned the birth certificates database by discarding records with implausible combinations of birth weight and gestational age (Alexander et al. 1996).

Our comparison of a subset of birth certificate data and hospital-based birth records collected for research purposes showed that birth certificates significantly underreported the incidence of maternal conditions such as preeclampsia (1.4% vs. 3.1%) and diabetes (2.0% vs. 5.6%) in this subset. An even more troublesome pattern we observed was the disproportionate underreporting of these complications in low-SES groups—a disparity that also probably holds for a more specific condition such as GDM. Because air pollution exposure is generally also higher in lower-SES groups than in better-off populations (a pattern that we also observed in the current study), such a disparate reporting pattern can introduce downward bias in the estimation of the associations between air pollution exposure and either preeclampsia or GDM. Our previous study reported significantly positive associations between air pollution exposure and the risk of preeclampsia using 1997–2006 birth record from the same four hospitals to which we compared the subset of birth certificate data (Wu et al. 2009b, 2011b). Although the

years did not match exactly between the previous study and this study (1997–2006 vs. 2001–2008), there was considerable overlap in time. In addition, most hospital records (94%) could be matched to the birth certificate data. Thus, we expected similar results (i.e., positive association between air pollution and preeclampsia) using 2001–2008 matched hospital data. Therefore, the many negative associations we observed between air pollution and these two pregnancy complications based on the birth certificate data may at least be partly explained by the disproportionate underreporting bias.

In addition, California birth certificates reported no diagnostic date of incidence for pregnancy conditions such as preeclampsia or GDM. This lack of information makes it difficult to disregard the influence of air pollution exposures that occurred after the incidence of the disease and which, therefore, could not have caused the condition. The lack of time data also makes it impossible to distinguish between early-onset and late-onset preeclampsia, which are suspected to have different etiologies and therefore might be differentially associated with air pollution (Dadvand et al. 2013a).

Potential Confounders

Several adjustments had relatively little impact on the analyses. For term LBW, preeclampsia, and GDM, adjustments for the trimester during which prenatal care began, chronic hypertension, diabetes, and the time of conception (using smoothing splines with 4 degrees of freedom per year) had little impact. (Appendix B, Table B.12; Appendix D, Table D.8; and Appendix E, Table E.2, show the sensitivity analyses for term LBW, preeclampsia, and GDM, respectively, adjusted for time of conception.) Nor did adjusting for the month of conception (in addition to the year of conception) substantially affect the association between air pollution and PTB (Appendix C, Table C.12). Similarly, smoking during pregnancy (in 2007–2008 data only; see Appendix B, Table B.11; Appendix C, Table C.11; and Appendix D, Table D.9) had a negligible impact on the analyses.

Some adjustments did have an effect on the associations between air pollution and pregnancy outcomes. Adjusting for temperature generally reduced the magnitude of the associations between O_3 and pregnancy outcomes (data not shown). Further adjustment for BMI (either using linear terms or polynomial functions) slightly reduced the associations between air pollutants and PTB and term LBW, but the magnitude of this reduction was limited (Appendix B, Table B.11, and Appendix C, Table C.11).

The negligible impact of adjusting for smoking or some chronic diseases might partly be due to the underreporting of these factors in birth certificates, leading to a very low proportion of women with such factors documented in the study population (0.4% for chronic hypertension, 2.9% for total diabetes, 2.5% for smoking in 2007–2008 data). For comparison, we retrieved the more recent California's Maternal and Infant Health Assessment Survey Study (California Department of Health Services–Tobacco Control Section 2006; Rinki et al. 2012) (Table 9). Although the survey was not conducted between the years 2007–2008, we expect that the true rate for these years is around 6% to 7%, assuming a linear decreasing trend between the years 1999 and 2010. The assumption seems reasonable if the California trend of smoking during pregnancy follows the trend of all smokers over 2000–2007 in the state (*www.cdc.gov/mmwr/preview/mmwrhtml/mm5809a1.htm*). Thus, we believe that the birth certificates underestimated maternal smoking rates by more than 50% (2.6% vs. 6–7%).

The underreporting of active smoking and the lack of data on passive smoking in California birth certificates are limitations in our study. We adjusted for the major determinants of smoking during pregnancy (age, race, education, SES) (Murin et al. 2011) and long-term temporal trends (California Department of Health Services–Tobacco Control Section 2006) as part of sensitivity analyses. These same factors may also be determinants of passive smoking (e.g., because of the overall likely similarity of socioeconomic characteristics of women and their family members, friends, and colleagues). Still, the possibility of residual confounding by active smoking, passive smoking, or both (because of incomplete data for smoking and a lack of data for passive smoking) cannot be excluded.

On the other hand, as shown in our causal diagram, further adjustment for smoking in addition to adjustment for maternal age, race/ethnicity, education, and neighborhood socioeconomic level might result in overadjustment bias (Greenland et al. 1999).

It is unclear whether the aforementioned phenomena of residual confounding and overadjustment bias are in play, and if so, what their respective magnitude and joint effects would be. Importantly, as already shown in Appendices B and C, adjusting for the imperfect smoking data in California birth certificates generally (except for O_3) slightly increased the ORs for term LBW and PTB. This is more suggestive of an overadjustment effect than of residual confounding, but the imperfect smoking data do not allow us to draw a firm conclusion on this issue.

The robustness of the positive associations between PTB and several sources and components of air pollution was tested as part of multipollutant analyses. The positive association between PTB and $PM_{2.5}$ was robust to adjustment for either NO_2 or O_3. When NO_2 and O_3 were both introduced into the same model, associations with PTB remained positive and significant for these two pollutants (Appendix C, Table C.13).

In sensitivity analyses adjusted for total $PM_{2.5}$, the positive associations between PTB and primary PM from specific sources disappeared, except for wood burning (Appendix C, Table C.14). The positive associations between PTB and PM components disappeared, except for ammonium and nitrates in $PM_{2.5}$ and SOA in $PM_{0.1}$ (Appendix C, Table C.14). In all the aforementioned multipollutant models, the positive association between total $PM_{2.5}$ and PTB remained robust to the adjustment for primary PM from each source or for PM components (Appendix C, Table C.14). However, considering that the mass of each PM component does contribute to the mass of total $PM_{2.5}$, the results of the aforementioned sensitivity analyses must be interpreted cautiously.

Statistical Analyses

Many statistical tests were applied as part of this study, with a (two-sided) 5% type I error risk for each. As a result, a proportion of the statistically significant associations observed (either positive or negative) are pure chance findings. However, because the accepted type 1 error risk was only 5%, chance findings cannot explain a large proportion of the significant associations we observed, whether they were positive (which was often the case for PTB and term LBW) or negative (which was often the case for preeclampsia and GDM).

We decided to use generalized additive mixed models (GAMMs) with random effects per hospital wherever feasible (i.e., for term LBW, preeclampsia, and GDM) to take into account possible differences of effects across hospitals, for example, reporting differences in the pregnancy outcomes. The potential for discrepancies in reporting was less of a concern for birth weight, which is easy to measure and report. It is likely that some GAMMs did not converge, especially in the smallest subgroups, because not enough observations occurred in certain hospitals. For the smallest subgroups (lowest education, African American mothers, etc.), inadequate numbers of observations was especially a factor. However, for a given pregnancy outcome and subgroup, models often converged for some pollutants but not for others. The reason for this pattern is unclear.

Unfortunately, no package in the R environment allows the introduction of random effects as part of conditional logistic regression (the method used for the PTB analyses). We tested the mclogit package (which allows for the introduction of random intercepts, but does not yet allow for random slopes). Although this package worked well on subsets of our data, unfortunately, it did not work for the whole data set in California, because of memory-size constraints.

General Limitations

Our study design includes some limitations that are common in the field. The personal exposure of mothers during pregnancy could not be estimated in this large cohort, and we had no time-activity information on individuals. These are limitations because pollution levels can vary substantially among microenvironments (e.g., workplace, public transportation) (Wu et al. 2011a). In addition, our air pollution metrics relied on maternal home address at the time of delivery because of a lack of data on residential history. All these sources of exposure measurement error contribute random error to the epidemiologic results and might also potentially generate bias.

COMPARISON WITH THE LITERATURE

Term Low Birth Weight

It may seem surprising that we did not observe any association between total $PM_{2.5}$ and term LBW, considering that a recent meta-analysis (Dadvand et al. 2013b), a

Table 9. Smoking during pregnancy among California woman[a]

	Year					
	1999	2000	2001	2002	2003	2010
Smoking during pregnancy (%)	11.6	9.8	10.6	9.0	8.7	5.6

[a]Data from California Department of Heath Services–Tobacco Control Section (2006) and Rinki et al. (2012).

major pooled analysis of European cohorts (Pedersen et al. 2013), and an analysis of a large World Health Organization database (Fleischer et al. 2014) all reported positive associations for this pollutant. However, because the composition of $PM_{2.5}$ is highly variable across time and space (Bell et al. 2007), heterogeneity of effects across settings is expected.

Only a few studies have investigated the relationship between PM composition in $PM_{2.5}$ and birth weight. Positive associations have been observed between term LBW and zinc, EC, silicon, aluminum, vanadium, and nickel (Bell et al. 2010). Bell and colleagues (2012) have also reported positive associations between LBW and potassium and titanium. Ebisu and Bell (2012) observed increased term LBW risk associated with aluminum, EC, nickel, and titanium. Basu and colleagues (2014) reported positive associations between term LBW and ammonium, iron, sulfates, titanium, zinc, and EC.

Unlike the aforementioned studies, which ascribed measurements from speciation monitors to subjects living within certain distances from the monitors, we used a chemical transport model. Despite the obvious advantages of this approach in better capturing the spatial variability in pollutant concentrations, the transport model may be limited in its ability to capture temporal variability because of the lack of temporal resolution of emission inventories or source profiles. This drawback of the model might partly explain the lack of positive associations observed between term LBW and chemical species in PM other than SOA (and nitrates, although the association was only close to significance for this pollutant, $P = 0.07$).

The positive association we observed between term LBW and O_3 is consistent with previous studies conducted in California (Laurent et al. 2013; Morello-Frosch et al. 2010; Salam et al. 2005). However, we observed no association between PAH and term LBW, in contrast to other authors who reported the associations with intrauterine growth restriction (Choi et al. 2012; Perera et al. 2005).

Analyses of PM by source revealed positive associations between term LBW and PM from most evaluated sources. These findings are supported by other studies for gasoline (Wilhelm et al. 2012), diesel (Slama et al. 2007; Wilhelm et al. 2012), traffic-related $PM_{2.5}$ (Bell et al. 2010), and commercial meat cooking (Choi and Perera 2012; Wilhelm et al. 2012). We have no straightforward explanation for the inverse association we observed with wood burning, which differs with findings from other studies (Boy et al. 2002; Thompson et al. 2011). However, wood burning is generally more frequent in rural areas, where greenness exposure is also higher. Greenness exposure was associated with higher birth weights in several recent studies (Dadvand et al. 2012a,b; Donovan et al. 2010; Laurent et al. 2013). Of interest in future studies is whether the inverse association between term LBW and wood burning persists after adjusting for greenness.

Positive associations were observed between term LBW and traffic-related primary pollutants or traffic sources characterized at a fine geographical resolution, although the associations with CALINE4 estimates were significant only in the small subgroup with the best geocoding accuracy. Our findings are consistent with those from previous studies, both for traffic density (Laurent et al. 2013; Malmqvist et al. 2011; Padula et al. 2012; Pedersen et al. 2013; Wilhelm and Ritz 2003; Zeka et al. 2008) and for distance to roadways (Brauer et al. 2008; Dadvand et al. 2014b; Genereux et al. 2008; Laurent et al. 2014; Miranda et al. 2013; van den Hooven et al. 2009; Yorifuji et al. 2012; Zeka et al. 2008).

Preterm Birth

We found a positive association between PTB and total measured $PM_{2.5}$. This finding is compatible with previously published literature (Kloog et al. 2012; Pereira et al. 2014; Stieb et al. 2012), although again, because the composition of $PM_{2.5}$ substantially varies in time and space, different findings from one setting to another are expected. Our $PM_{2.5}$ finding is consistent with a previous study conducted in California by other investigators during an earlier period (1999–2000) (Huynh et al. 2006).

Positive associations were also observed with primary pollutants such as EC in PM; the finding is consistent with a previous study based on speciation monitor measurements in Los Angeles (Wilhelm et al. 2011). A positive association was also observed with NO_2 interpolated by EBK at the scale of the entire state of California, but not in Los Angeles, where NO_2 was estimated using a spatiotemporal model. Although this finding was unexpected, other investigators also reported a negative association between NO_2 modeled using a time-adjusted land-use regression model and PTB in Los Angeles (Wilhelm et al. 2011). We did not observe any association between PTB and PAH exposure in our study in Los Angeles, contrary to some previous studies (Choi et al. 2008; Padula et al. 2014; Wilhelm et al. 2011).

We found primary PM from several sources to be positively associated with PTB. Consistent findings have been reported previously from other studies for diesel sources and commercial meat cooking (Wilhelm et al. 2011); wood burning (Wylie et al. 2014); or biomass burning (Wilhelm et al. 2011), although these studies used different methodologies. The positive association we observed with wood burning was very small. Until our present study, no other

study had identified any significant positive association with gasoline (Huppe et al. 2013; Wilhelm et al. 2011).

We also found an increased risk of PTB with exposure to O_3 (consistent with some previous studies [Olsson et al. 2013] but not all of them [Stieb et al. 2012]) and other secondary pollutants such as SOA, nitrates, and ammonium. A recent study in Los Angeles County reported a positive association between PTB and measured ammonium nitrate in $PM_{2.5}$ (Wilhelm et al. 2011). The association is clearly consistent with our results, because ammonium and nitrates are highly correlated in California ($r = 0.95$). However, another study in Atlanta used a time-series methodology and reported no association between PTB and nitrates or ammonium (Darrow et al. 2009). This same study reported a positive association with sulfates, a pollutant with higher concentrations in the eastern United States than in the western part of the country (Bell et al. 2007) and for which the modeling performance was suboptimal in our study setting (Hu et al. 2015).

Interestingly, our findings for the associations between PTB and traffic-related pollution characterized at a fine geographical resolution using predictions from the CALINE4 model for traffic density, road length, and distance to roads are highly sensitive to the accuracy of geocoding. Although associations were either null or negative when the entire population was considered, we did observe some positive associations when we only considered the births geocoded with better accuracy. If an increase in PTB risk truly occurs only within a short distance from roads (e.g., less than 150 m), as our results suggest, then imprecise geocoding could easily introduce substantial exposure measurement error, obscuring any epidemiological associations with local traffic emissions.

The problem of imprecise geocoding might help explain some inconsistent findings from the literature, although many studies have reported positive associations between PTB and traffic exposure (Miranda et al. 2013; Yang et al. 2003; Yorifuji et al. 2011). Researchers might need to make a trade-off between the need for sufficient geocoding accuracy and the need for an adequate sample size to allow for the detection of increased risks associated with traffic exposure (Laurent et al. 2013).

Preeclampsia

Our findings of an inverse association between preeclampsia and ambient air pollutant concentrations conflict with those from most previously published studies (Pedersen et al. 2014), including a study of our own that was conducted in four hospitals in Los Angeles and Orange Counties in California but was based on hospital records for research purposes (Wu et al. 2011b). In addition to the differential reporting rates according to SES and the likely resulting bias, other potential explanations should be considered. Although the etiology of preeclampsia remains mostly unknown (Steegers et al. 2010), maternal cigarette smoking has been consistently shown to be inversely associated with preeclampsia. This inverse relationship seems counterintuitive, especially because maternal smoking is an established risk factor for PTB, term LBW, and many other adverse conditions such as cancer and cardiovascular diseases (England and Zhang 2007). Some researchers have hypothesized that CO might be responsible for this protective association (Karumanchi and Levine 2010). Among studies that investigated the association between ambient CO levels resulting from traffic-related emissions, some, but not all, reported a negative association with preeclampsia (Zhai et al. 2012). We indeed observed a negative association between preeclampsia and CO modeled with CALINE4, but this was significant only in the population subset with medium geocoding accuracy.

Because CO and primary EC from traffic are likely to be highly correlated, we suspect that the inverse association between preeclampsia and EC might be influenced by a protective effect of CO. In addition, the apparently protective association from O_3 might be the marker of a higher vitamin D status, which is protective against preeclampsia (Tabesh et al. 2013). Sunshine is important in both O_3 and vitamin D production. Although there was a slight negative correlation between sulfates and O_3 ($r = -0.15$), the highest sulfate concentration was observed in the summertime (although a lower peak may also be observed in winter). This suggests that the inverse association between sulfates and preeclampsia might also partly be explained by a protective effect of vitamin D in the summertime.

Gestational Diabetes Mellitus

Only three other studies have examined the association between air pollution and GDM. A study embedded in the Generation R Study cohort in the Netherlands found no association between residential proximity to traffic and GDM (van den Hooven et al. 2009). Researchers in southern Sweden reported an increased risk of GDM from NO_x exposure, with an adjusted OR of 1.69 (95% CI: 1.41–2.03) for the highest quartile of exposure (> 22.7 μg/m^3) compared with the lowest quartile (2.5–8.9 μg/m^3), during the second trimester (Malmqvist et al. 2013). Another study in Massachusetts found no association between air pollution exposure and GDM, but it reported an increased risk of impaired glucose tolerance with elevated exposure to $PM_{2.5}$ and traffic density (Fleisch et al. 2014).

CONCLUSIONS

We observed a positive association between total measured $PM_{2.5}$ and PTB, but not term LBW. Both PTB and term LBW are associated with some primary components of ambient air pollution, notably, primary PM from traffic emissions and commercial meat cooking. PTB is also associated with NO_2, with EC, and, though more weakly, with PM from wood burning. Exposure to EC during the last trimester of pregnancy was also positively associated with term LBW.

Regarding secondary pollutants, O_3 and SOA were positively associated with both term LBW and PTB. Nitrates and ammonium were positively associated with PTB and term LBW (but only for exposure averaged on the last trimester of pregnancy for term LBW). OC was positively associated with PTB but not term LBW.

Stronger associations between primary pollutants and birth outcomes were observed in several population subgroups. For both PTB and term LBW, the strongest associations were typically observed in mothers with low educational level or chronic hypertension. For PTB only, stronger associations were typically found in mothers living in poorer neighborhoods, African Americans and Hispanics, and women with a higher BMI at the beginning of pregnancy. Patterns according to subgroups were generally less striking for secondary pollutants.

Many negative associations were observed between air pollution indicators and either preeclampsia or GDM. These findings might be influenced by the substantial underreporting of preeclampsia and diabetes in birth certificate data, especially the higher rates of underreporting in more socioeconomically deprived populations.

IMPLICATIONS OF FINDINGS

- This large study consistently linked term LBW with traffic-related pollution from different exposure indicators. PTB was also positively associated with traffic-related pollutants, although positive associations with some indicators of traffic-related pollution at fine geographic scale were only apparent at the better levels of geocoding accuracy. Altogether, these findings suggest, in accordance with most previously published literature, the importance of limiting exposure of pregnant women to traffic pollution to prevent these adverse pregnancy outcomes. Associations observed with PM from commercial meat cooking for both LBW and PTB, and a modest association with wood burning for PTB, suggest the importance of further studying the impact of these sources, which are widespread in the environment. Primary PM from other sources not included in the current study (e.g., industrial emissions, shipping, and airports) would also be worthy of further investigation, but more effort is needed to validate the modeling of PM exposure from these sources.
- Also associated with increased risk of PTB or term LBW were secondary pollutants, especially ammonium, nitrates, O_3, and SOA. Understanding and modeling the chemistry of secondary air pollutants are challenging tasks. It is still unclear whether these components are actually the causal agents leading to these adverse pregnancy outcomes or if they are only correlated with the outcomes. Altogether, however, these results point to the importance of further study on the effects of secondary air pollutants on pregnancy outcomes.
- This study suggests that several subgroups of pregnant women are more sensitive to exposure to primary pollutants. In general, the more sensitive subgroups include women with a lower education background, those living in poorer neighborhoods, and women with chronic hypertension. Women with a high BMI and African Americans and Hispanics were also more at risk of PTB associated with primary air pollutants. These results suggest that to reduce adverse pregnancy outcomes associated with primary air pollutants, top consideration should be given to targeting the neighborhoods where these susceptible populations live.
- This study suggests that the retrospective information available on maternal conditions such as preeclampsia or GDM in California birth certificates is probably inadequate for studies on the effects of air pollution on these conditions. Unless the reporting of maternal conditions on birth certificates dramatically improves, or unless birth certificates have some sort of linkage with other routine health databases for more efficient identification of these conditions, research projects are better served when they use records specifically collected within the framework of the research.

ACKNOWLEDGMENTS

We acknowledge the funding from the National Institute of Environmental Health Sciences (NIEHS R21ES016379) for the collection of NO_2 and PAH data in Los Angeles and Orange Counties. Addition collection of

NO_2 data by UCLA researchers was funded by California Air Resources Board (Contract No. 04-323). We thank the study subjects and volunteers who participated in the air pollution exposure sampling.

We also thank the Health Information and Research Section/California Department of Public Health for providing birth certificate data; the California Air Resources Board for providing long-term meteorological data; Judith Chung (UC–Irvine) for her help in obtaining hospital-based Memorial Care birth records; Jane Berner (California Department of Transportation) for her help in retrieving the PeMS traffic count data; Cristina Milesi (California State University Monterey Bay/NASA Ames Research Center) for providing NDVI data in California; and Kimberly Clark (Southern California Association of Government) for providing 2008 land-use data.

Concentration fields predicted by the UCD/CIT model were supported by the US EPA (Project R83386401) and the California Air Resources Board (Project 10-319). This research has not been subject to the EPA's required peer and policy review and therefore does not necessarily reflect the views of the agency; no official endorsement should be inferred.

The authors thank Beate Ritz (UCLA) and Ralph Delfino (UCI) for initiating the study and for providing important data for exposure model development and validation. We also thank Myles Cockburn (USC) and Loraine Escobedo (USC) for geocoding all the birth certificate data. We acknowledge Scott Bartell (UC–Irvine) for providing some advice on statistical analyses and Andy Dang (UC–Irvine), who contributed to field data collection. In addition, we appreciate our conversations with Tim-Allen Bruckner (UC–Irvine), who provided useful information on birth weight. Finally, we appreciate the help of staff at the High-Performance Computing Cluster (Harry Mangalam, Adam Brenner, at Joseph Farran) at UC–Irvine for accommodating the computational needs of this project.

REFERENCES

Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. 1996. A United States national reference for fetal growth. Obstet Gynecol 87:163–168.

Araujo JA, Barajas B, Kleinman M, Wang X, Bennett BJ, Gong KW, et al. 2008. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res 102:589–596.

Basu R, Harris M, Sie L, Malig B, Broadwin R, Green R. 2014. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. Environ Res 128:42–51.

Bell ML, Belanger K, Ebisu K, Gent JF, Leaderer BP. 2012. Relationship between birth weight and exposure to airborne fine particulate potassium and titanium during gestation. Environ Res 117:83–89.

Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P, et al. 2010. Prenatal exposure to fine particulate matter and birth weight variations by particulate constituents and sources. Epidemiology 21:884–891.

Bell ML, Dominici F, Ebisu K, Zeger SL, Samet JM. 2007. Spatial and temporal variation in $PM_{2.5}$ chemical composition in the United States for health effects studies. Environ Health Perspect 115:989–995.

Benson P. 1989. Caline4: A Dispersion Model for Predicting Air Pollutant Concentrations near Roadways. FHWA-CA-TL-84-15. Sacramento, CA:California Department of Transportation.

Boy E, Bruce N, Delgado H. 2002. Birth weight and exposure to kitchen wood smoke during pregnancy in rural Guatemala. Environ Health Perspect 110:109–114.

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116:680–686.

California Air Resources Board. 2013. Mobile Source Emission Inventory: Current Methods and Data. Available: *www.arb.ca.gov/msei/modeling.htm.*

California Department of Health Services—Tobacco Control Section. 2006. Smoking During Pregnancy. Available: *www.cdph.ca.gov/programs/tobacco/Documents/Archived%20Files/CTCPPregnancy06.pdf* [accessed 15 July 2015].

Carlton AG, Bhave PV, Napelenok SL, Edney ED, Sarwar G, Pinder RW, et al. 2010. Model representation of secondary organic aerosol in CMAQv4.7. Environ Sci Technol 44:8553–8560.

Carter WPL, Heo G. 2012. Development of Revised SAPRC Aromatics Mechanisms. Final Report to California Air Resources Board, Contracts No. 07-730 and 08-326. Riverside, CA:University of California Center for Environmental Reseach and Technology.

Carter WPL, Heo G. 2013. Development of revised SAPRC aromatics mechanisms. Atmos Environ 77:404–414.

Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, et al. 2007. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA birth cohort. Am J Respir Crit Care Med 175:1078–1085.

Centers for Disease Control and Prevention. 1999. Preterm Singleton Births—United States, 1989–1996. Available: *www.cdc.gov/mmwr/preview/mmwrhtml/00056645.htm* [accessed 20 November 2013].

Centers for Disease Control and Prevention. 2002. Infant Mortality and Low Birth Weight among Black and White Infants—United States, 1980–2000. Available: *www.cdc.gov/mmwr/preview/mmwrhtml/mm5127a1.htm* [accessed 20 November 2013].

Chen JJ, Ying Q, Kleeman MJ. 2010. Source apportionment of wintertime secondary organic aerosol during the California Regional $PM_{10}/PM_{2.5}$ Air Quality Study. Atmos Environ 44:1331–1340.

Chen Z, Du J, Shao L, Zheng L, Wu M, Ai M, et al. 2009. Prepregnancy body mass index, gestational weight gain, and pregnancy outcomes in China. Int J Gynaecol Obstet 109(1):41–44.

Chernausek SD. 2012. Update: consequences of abnormal fetal growth. J Clin Endocrinol Metab 97:689–695.

Choi H, Perera FP. 2012. Sources of greater fetal vulnerability to airborne polycyclic aromatic hydrocarbons among African Americans. J Epidemiol Community Health 66:121–126.

Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. 2008. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. Environ Health Perspect 116:658–665.

Choi H, Wang L, Lin XH, Spengler JD, Perera FP. 2012. Fetal window of vulnerability to airborne polycyclic aromatic hydrocarbons on proportional intrauterine growth restriction. PLoS ONE 7; doi: 10.1371/journal.pone.0035464.

Christakos G. 1990. A Bayesian maximum entropy view to the spatial estimation problem. Math Geol 22:763–777.

Chu SY, Kim SY, Bish CL. 2009. Prepregnancy obesity prevalence in the United States, 2004–2005. Matern Child Health J 13:614–620.

Dadvand P, de Nazelle A, Figueras F, Basagana X, Su J, Amoly E, et al. 2012a. Green space, health inequality and pregnancy. Environ Int 40:110–115.

Dadvand P, Figueras F, Basagana X, Beelen R, Martinez D, Cirach M, et al. 2013a. Ambient air pollution and preeclampsia: a spatiotemporal analysis. Environ Health Perspect 121:1365–1371.

Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. 2013b. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 121:367–373.

Dadvand P, Ostro B, Amato F, Figueras F, Minguillon MC, Martinez D, et al. 2014a. Particulate air pollution and preeclampsia: a source-based analysis. Occup Environ Med 71:570–577.

Dadvand P, Ostro B, Figueras F, Foraster M, Basagana X, Valentin A, et al. 2014b. Residential proximity to major roads and term low birth weight: the roles of air pollution, heat, noise, and road-adjacent trees. Epidemiology 25:518–525.

Dadvand P, Sunyer J, Basagana X, Ballester F, Lertxundi A, Fernandez-Somoano A, et al. 2012b. Surrounding greenness and pregnancy outcomes in four Spanish birth cohorts. Environ Health Perspect 120:1481–1487.

Darrow LA, Klein M, Flanders WD, Waller LA, Correa A, Marcus M, et al. 2009. Ambient air pollution and preterm birth: a time-series analysis. Epidemiology 20:689–698.

Darrow LA, Klein M, Strickland MJ, Mulholland JA, Tolbert PE. 2011. Ambient air pollution and birth weight in full-term infants in Atlanta, 1994–2004. Environ Health Perspect 119:731–737.

Delfino RJ, Staimer N, Tjoa T, Arhami M, Polidori A, Gillen DL, et al. 2010. Association of biomarkers of systemic inflammation with organic components and source tracers in quasi-ultrafine particles. Environ Health Perspect 118:756–762.

Donovan GH, Michael YL, Butry DT, Sullivan AD, Chase JM. 2010. Urban trees and the risk of poor birth outcomes. Health & Place 17(1):390–393.

Dzhambov AM, Dimitrova DD, Dimitrakova ED. 2014. Noise exposure during pregnancy, birth outcomes and fetal development: meta-analyses using quality effects model. Folia Med (Plovdiv) 56:204–214.

Ebisu K, Bell ML. 2012. Airborne $PM_{2.5}$ chemical components and low birth weight in the Northeastern and Mid-Atlantic regions of the United States. Environ Health Perspect 120:1746–1752.

England L, Zhang J. 2007. Smoking and risk of preeclampsia: a systematic review. Front Biosci 12:2471–2483.

Fan ZH, Jung KH, Lioy PJ. 2006. Development of a passive sampler to measure personal exposure to gaseous PAHs in community settings. Environ Sci Technol 40:6051–6057.

Ferrara A. 2007. Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care 30 Suppl 2:S141–146.

Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. 2006. Consequences of fetal exposure to maternal diabetes in offspring. J Clin Endocrinol Metab 91:3718–3724.

Fleisch AF, Gold DR, Rifas-Shiman SL, Koutrakis P, Schwartz JD, Kloog I, et al. 2014. Air pollution exposure and abnormal glucose tolerance during pregnancy: the Project Viva cohort. Environ Health Perspect 122:378–383.

Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP, et al. 2014. Outdoor air pollution, preterm birth, and low birth weight: analysis of the World Health Organization Global Survey on Maternal and Perinatal Health. Environ Health Perspect 122: 425–430.

Gehring U, Tamburic L, Simi H, Davies HW, Brauer M. 2014. Impact of noise and air pollution on pregnancy outcomes. Epidemiology 25:351–358.

Genereux M, Auger N, Goneau M, Daniel M. 2008. Neighbourhood socioeconomic status, maternal education and adverse birth outcomes among mothers living near highways. J Epidemiol Community Health 62:695–700.

Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. 2004. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology 15:36–45.

Goldberg D. 2011a. The USC WebGIS Geocoding Platform—GIS Research Laboratory Research Report No. 11. Los Angeles, CA:University of Southern California.

Goldberg DW. 2011b. Improving geocoding match rates with spatially-varying block metrics. Transactions in GIS 15:829–850.

Greenland S, Pearl J, Robins JM. 1999. Causal diagrams for epidemiologic research. Epidemiology 10:37–48.

Gribov A, Krivoruchko K. 2012. Quantitative geology and geostatistics. In: New Flexible Nonparametric Data Transformation for Transgaussian Kriging, Vol. 17. Netherlands:Springer.

Ham WA, Kleeman MJ. 2011. Size-resolved source apportionment of carbonaceous particulate matter in urban and rural sites in central California. Atmos Environ 45:3988–3995.

Herner JD, Aw J, Gao O, Chang DP, Kleeman MJ. 2005. Size and composition distribution of airborne particulate matter in Northern California: I-particulate mass, carbon, and water-soluble ions. J Air Waste Manage 55:30–51.

Hu JL, Zhang HL, Chen SH, Wiedinmyer C, Vandenberghe F, Ying Q, et al. 2014a. Predicting primary PM2.5 and PM0.1 trace composition for epidemiological studies in California. Environ Sci Technol 48:4971–4979.

Hu JL, Zhang HL, Chen SH, Ying Q, Wiedinmyer C, Vandenberghe F, et al. 2014b. Identifying PM2.5 and PM0.1 sources for epidemiological studies in California. Environ Sci Technol Environ Sci Technol 48:4980–4990.

Hu J, Zhang H, Ying Q, Chen SH, Vandenberghe F, Kleeman MJ. 2015. Long-term particulate matter modeling for health effect studies in California. Part 1: model performance on temporal and spatial variations. Atmos Chem Phys 15:3445–3461.

Huppe V, Kestens Y, Auger N, Daniel M, Smargiassi A. 2013. Residential proximity to gasoline service stations and preterm birth. Environ Sci Pollut Res Int 20:7186–7193.

Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. 2006. Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol 20:454–461.

Jeng HA. 2010. Chemical composition of ambient particulate matter and redox activity. Environ Monit Assess 169:597–606.

Karumanchi SA, Levine RJ. 2010. How does smoking reduce the risk of preeclampsia? Hypertension 55:1100–1101.

Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. 2007. Gestational weight gain and pregnancy outcomes in obese women: how much is enough? Obstet Gynecol 110:752–758.

Kim S, Shen S, Sioutas C, Zhu YF, Hinds WC. 2002. Size distribution and diurnal and seasonal trends of ultrafine particles in source and receptor sites of the Los Angeles Basin. J Air Waste Manage 52:297-307.

Kleeman MJ, Cass GR. 2001. A 3d Eulerian source-oriented model for an externally mixed aerosol. Environ Sci Technol 35:4834–4848.

Kleeman MJ, Cass GR, Eldering A. 1997. Modeling the airborne particle complex as a source-oriented external mixture. J Geophys Res Atmos 102:21355–21372.

Kleeman MJ, Riddle SG, Robert MA, Jakober CA, Fine PM, Hays MD, et al. 2009. Source apportionment of fine (PM1.8) and ultrafine (PM0.1) airborne particulate matter during a severe winter pollution episode. Environ Sci Technol 43:272–279.

Kleeman MJ, Ying Q, Lu J, Mysliwiec MJ, Griffin RJ, Chen JJ, et al. 2007. Source apportionment of secondary organic aerosol during a severe photochemical smog episode. Atmos Environ 41:576–591.

Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. 2012. Using new satellite based exposure methods to study the association between pregnancy PM(2.5) exposure, premature birth and birth weight in Massachusetts. Environ Health 11:40; doi:10.1186/1476-069X-11-40.

Krishnamoorthy U, Schram CM, Hill SR. 2006. Maternal obesity in pregnancy: is it time for meaningful research to inform preventive and management strategies? BJOG 113:1134–1140.

Krivoruchko K. 2012. Empirical Bayesian Kriging, Implemented in ArcGIS Geostatistical Analyst (ArcGIS User Conference 2012). ESRI. Available: *www.esri.com/news/arcuser/1012/files/ebk.pdf* [accessed 3 June 2016].

Krudysz MA, Froines JR, Fine PM, Sioutas C. 2008. Intra-community spatial variation of size-fractionated PM mass, OC, EC, and trace elements in the Long Beach, CA area. Atmos Environ 42:5374–5389.

Lacasana M, Esplugues A, Ballester F. 2005. Exposure to ambient air pollution and prenatal and early childhood health effects. Eur J Epidemiol 20:183–199.

Laurent O, Hu J, Li L, Cockburn M, Escobedo L, Kleeman MJ, et al. 2014. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ Res 134:488–495.

Laurent O, Wu J, Li LF, Chung J, Bartell S. 2013. Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ Health 12:18; doi:10.1186/1476-069X-12-18.

Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B. 2013. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J 17:545–555.

Li LF, Wu J, Ghosh JK, Ritz B. 2013. Estimating spatiotemporal variability of ambient air pollutant concentrations with a hierarchical model. Atmos Environ 71:54–63.

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111:455–460.

Lindstrom J, Szpiro AA, Sampson DP, Sheppard L, Oron A, Richards M, et al. 2011. A flexible spatio-temporal model for air pollution: allowing for spatio-temporal covariates. UW Biostatistics Working Paper Series; Working Paper 370. Seattle, WA:University of Washington.

Maisonet M, Correa A, Misra D, Jaakkola JJ. 2004. A review of the literature on the effects of ambient air pollution on fetal growth. Environ Res 95:106–115.

Malmqvist E, Jakobsson K, Tinnerberg H, Rignell-Hydbom A, Rylander L. 2013. Gestational diabetes and preeclampsia in association with air pollution at levels below current air quality guidelines. Environ Health Perspect 121:488–493.

Malmqvist E, Rignell-Hydbom A, Tinnerberg H, Bjork J, Stroh E, Jakobsson K, et al. 2011. Maternal exposure to air pollution and birth outcomes. Environ Health Perspect 119:553–558.

Masek JG, Vermote EF, Saleous N, Wolfe R, Hall FG, Huemmrich F, et al. 2012. LEDAPS Landsat calibration, reflectance, atmospheric correction preprocessing code. Model product. Available: *http://Dx.Doi.Org/10.3334/Ornldaac/1080* [accessed 3 June 2016].

Miranda ML, Edwards SE, Chang HH, Auten RL. 2013. Proximity to roadways and pregnancy outcomes. J Expo Sci Environ Epidemiol 23:32–38.

Morello-Frosch R, Jesdale BM, Sadd JL, Pastor M. 2010. Ambient air pollution exposure and full-term birth weight in California. Environ Health 9:44; doi:10.1186/1476-069X-9-44.

Murin S, Rafii R, Bilello K. 2011. Smoking and smoking cessation in pregnancy. Clin Chest Med 32:75–91, viii.

Mysliwiec MJ, Kleeman MJ. 2002. Source apportionment of secondary airborne particulate matter in a polluted atmosphere. Environ Sci Technol 36:5376–5384.

Nohr EA, Vaeth M, Baker JL, Sorensen TI, Olsen J, Rasmussen KM. 2009. Pregnancy outcomes related to gestational weight gain in women defined by their body mass index, parity, height, and smoking status. Am J Clin Nutr 90:1288–1294.

Ntziachristos L, Froines JR, Cho AK, Sioutas C. 2007. Relationship between redox activity and chemical speciation of size-fractionated particulate matter. Part Fibre Toxicol 4:5.

Olsson D, Mogren I, Forsberg B. 2013. Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. BMJ Open 3(2); doi:10.1136/bmjopen-2012-001955.

Padula AM, Mortimer K, Hubbard A, Lurmann F, Jerrett M, Tager IB. 2012. Exposure to traffic-related air pollution during pregnancy and term low birth weight: estimation of causal associations in a semiparametric model. Am J Epidemiol 176:815–824.

Padula AM, Noth EM, Hammond SK, Lurmann FW, Yang W, Tager IB, et al. 2014. Exposure to airborne polycyclic aromatic hydrocarbons during pregnancy and risk of preterm birth. Environ Res 135:221–226.

Park M, Stenstrom KM. 2008. Classifying environmentally significant urban land uses with satellite imagery. J Environ Manage 86:181–192.

Paul SR, Donner A. 1989. A comparison of tests of homogeneity of odds ratios in K 2 × 2 tables. Stat Med 8:1455–1468.

Pearl M, Wier ML, Kharrazi M. 2007. Assessing the quality of last menstrual period date on California birth records. Paediatr Perinat Epidemiol 21 Suppl 2:50–61.

Pedersen M, Giorgi-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F, et al. 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med 1:695–704.

Pedersen M, Stayner L, Slama R, Sorensen M, Figueras F, Nieuwenhuijsen MJ, et al. 2014. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. Hypertension 64:494–500.

Pereira G, Belanger K, Ebisu K, Bell ML. 2014. Fine particulate matter and risk of preterm birth in Connecticut in 2000–2006: a longitudinal study. Am J Epidemiol 179:67–74.

Pereira G, Haggar F, Shand AW, Bower C, Cook A, Nassar N. 2013. Association between pre-eclampsia and locally derived traffic-related air pollution: a retrospective cohort study. J Epidemiol Community Health 67:147–152.

Perera FP, Tang DL, Rauh V, Lester K, Tsai WY, Tu YH, et al. 2005. Relationships among polycyclic aromatic hydrocarbon-DNA adducts, proximity to the World Trade Center, and effects on fetal growth. Environ Health Perspect 113:1062–1067.

Ramachenderan J, Bradford J, McLean M. 2008. Maternal obesity and pregnancy complications: a review. Aust N Z J Obstet Gynaecol 48:228–235.

Rinki C, Martin K, Curtis M. 2012. 2010 Miha Regional Report: A Summary Report of Regional Snapshots and Geographic Comparisons from the Maternal and Infant Health Assessment Survey. Sacramento, CA:California Department of Public Health, Maternal, Child and Adolescent Health Program.

Ristovska G, Laszlo HE, Hansell AL. 2014. Reproductive outcomes associated with noise exposure—a systematic review of the literature. Int J Environ Res Public Health 11:7931–7952.

Ritz B, Wilhelm M. 2008. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin Pharmacol Toxicol 102:182–190.

Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA. 2011. Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in Western Washington State. Environ Health Perspect 119:886–892.

Saigal S, Doyle LW. 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 371:261–269.

Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. 2005. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect 113:1638–1644.

Sardar SB, Fine PM, Sioutas C. 2005a. Seasonal and spatial variability of the size-resolved chemical composition of particulate matter (PM_{10}) in the Los Angeles Basin. J Geophys Res-Atmos 110, D07S08, doi:10.1029/2004JD004627.

Sardar SB, Fine PM, Mayo PR, Sioutas C. 2005b. Size-fractionated measurements of ambient ultrafine particle chemical composition in Los Angeles using the Nano-MOUDI. Environ Sci Technol 39:932–944.

Schlesinger RB, Kunzli N, Hidy GM, Gotschi T, Jerrett M. 2006. The health relevance of ambient particulate matter characteristics: coherence of toxicological and epidemiological inferences. Inhal Toxicol 18:95–125.

Siega-Riz AM, Siega-Riz AM, Laraia B. 2006. The implications of maternal overweight and obesity on the course of pregnancy and birth outcomes. Matern Child Health J 10:S153–156.

Skamarock WC, Klemp JB, Dudhia J, O Gill D, Barker DM, Duda MG, et al. 2008. A Description of the Advanced Research WRF Version 3. NCAR Technical Note NCAR/TN-475+STR, June 2008.

Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann HE, et al. 2007. Traffic-related atmospheric pollutants levels during pregnancy and offspring's term birth weight: a study relying on a land-use regression exposure model. Environ Health Perspect 115:1283–1292.

Srám RJ, Binkova B, Dejmek J, Bobak M. 2005. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 113:375–382.

Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. 2010. Pre-eclampsia. Lancet 376:631–644.

Stieb DM, Chen L, Eshoul M, Judek S. 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ Res 117:100–111.

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. 2008. Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci 15:631–650.

Szpiro AA, Sampson DP, Sheppard L, Lumley T, Adar DS, Kaufman DJ. 2010. Predicting intra-urban variation in air pollution concentrations with complex spatio-temporal dependencies. Environmetrics 21:606–631.

Tabesh M, Salehi-Abargouei A, Tabesh M, Esmaillzadeh A. 2013. Maternal Vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. J Clin Endocrinol Metab 98:3165–3173.

Tele Atlas. 2010. Tele Atlas® MultiNet® 3.5.1 User Guide 2010. Available: *ftp://ftp.odot.state.or.us/region1/chi/TomTom/TomTomUserGuide.pdf* [accessed 19 May 2016].

Thompson LM, Bruce N, Eskenazi B, Diaz A, Pope D, Smith KR. 2011. Impact of reduced maternal exposures to wood smoke from an introduced chimney stove on newborn birth weight in rural Guatemala. Environ Health Perspect 119:1489–1494.

Tucker CJ. 1979. Red and photographic infrared linear combinations for monitoring vegetation. Remote Sensing Environ 8:127–150.

U.S. Census Bureau, 2000. Census 2000 data. Available: *www.census.gov/main/www/cen2000.html* [accessed 19 May 2016].

van den Hooven EH, Jaddoe VW, de Kluizenaar Y, Hofman A, Mackenbach JP, Steegers EA, et al. 2009. Residential traffic exposure and pregnancy-related outcomes: a prospective birth cohort study. Environ Health 8:59.

Villeneuve PJ, Jerrett M, Su JG, Burnett RT, Chen H, Wheeler AJ, et al. 2012. A cohort study relating urban green space with mortality in Ontario, Canada. Environ Res 115:51–58.

Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. 2012. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatr Perinat Epidemiol 26:91–100.

Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. 2011. Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles County, California. Environ Health 10:89.

Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. 2012. Traffic-related air toxics and term low birth weight in Los Angeles County, California. Environ Health Perspect 120:132–138.

Wilhelm M, Ritz B. 2003. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994–1996. Environ Health Perspect 111:207–216.

Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. 2009. Methodological issues in studies of air pollution and reproductive health. Environ Res 109:311–320.

World Health Organization. 2011. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Available: *www.who.int/reproductivehealth/publications/maternal_perinatal_health/program-action-eclampsia/en/* [accessed 3 June 2016].

World Health Organization MoD, PMNCH, and Save the Children. 2012. Born Too Soon: The Global Action Report on Preterm Birth (Howson CP, Kinney MV, Lawn JE, eds). Geneva, Switzerland:World Health Organization.

Wu J, Houston D, Lurmann F, Ong P, Winer A. 2009a. Exposure of $PM_{2.5}$ and EC from diesel and gasoline vehicles in communities near the Ports of Los Angeles and Long Beach, California. Atmos Environ 43:1962–1971.

Wu J, Jiang C, Houston D, Baker D, Delfino R. 2011a. Automated time activity classification based on global positioning system (GPS) tracking data. Environ Health 10:101.

Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. 2009b. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast Air Basin of California. Environ Health Perspect 117:1773–1779.

Wu J, Wilhelm M, Chung J, Ritz B. 2011b. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res 111:685–692.

Wylie BJ, Coull BA, Hamer DH, Singh MP, Jack D, Yeboah-Antwi K, et al. 2014. Impact of biomass fuels on pregnancy outcomes in central East India. Environ Health 13:1.

Xia T, Korge P, Weiss JN, Li N, Venkatesen MI, Sioutas C, et al. 2004. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. Environ Health Perspect 112:1347–1358.

Xu XH, Hu H, Ha S, Roth J. 2014. Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health 68:13–20.

Yale Center for Earth Observation (YCEO). 2010. Converting Landsat TM and ETM+ Thermal Bands to Temperature. Yale Center for Earth Observation. New Haven, CT:Yale University.

Yang CY, Chang CC, Chuang HY, Ho CK, Wu TN, Tsai SS. 2003. Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan. Arch Environ Health 58:649–654.

Yorifuji T, Naruse H, Kashima S, Ohki S, Murakoshi T, Takao S, et al. 2011. Residential proximity to major roads and preterm births. Epidemiology 22:74–80.

Yorifuji T, Naruse H, Kashima S, Murakoshi T, Tsuda T, Doi H, et al. 2012. Residential proximity to major roads and placenta/birth weight ratio. Sci Total Environ 414:98–102.

Yuan Y, Zhu Y, Wu J. 2011. Vehicular emitted ultrafine particle concentration and exposure spatial profile in Corpus Christi, Texas. Chemical Prod Proc Model 6:Article 8.

Zeka A, Melly SJ, Schwartz J. 2008. The effects of socioeconomic status and indices of physical environment on reduced birth weight and preterm births in Eastern Massachusetts. Environ Health 7:60.

Zhai DS, Guo YF, Smith G, Krewski D, Walker M, Wen SW. 2012. Maternal exposure to moderate ambient carbon monoxide is associated with decreased risk of preeclampsia. Am J Obstet Gynecol 207:57–59.

HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by Mr. David Bush of T&B Systems, Inc. Mr. Bush is an expert in quality assurance for air quality monitoring studies and data management. The audits included an on-site review of study activities for conformance to the study protocol and operating procedures. The dates of the audits are listed below with the phase of the study examined.

SEPTEMBER 18–19, 2014

An on-site audit was conducted at the University of California–Irvine. The audit concentrated on the study's analytical and data management activities and included an audit of the study's database. Several data points were traced through the entire data processing sequence to verify the integrity of the database. No significant issues were noted during the audit.

MARCH 2016

The final report was reviewed for internal consistency and description of data quality and quality control procedures. The review included a detailed review of the data set and processing files associated with the analysis of ozone versus term low birth weight, which effectively demonstrated the analytical process used during the study. No significant issues were noted.

Written reports of each inspection were provided to the HEI project manager, who transmitted the findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by an experienced team with a high concern for data quality. Study personnel were very responsive to audit questions, with no issues noted. The report appears to be an accurate representation of the study.

David H. Bush, Quality Assurance Officer

MATERIALS AVAILABLE ON THE WEB

Appendices A, B, C, D, and E contain supplemental material not included in the printed report. They are available on the HEI Web site *http://pubs.healtheffects.org*.

Appendix A. Procedures to Fill in Missing Weekly Concentrations of NO_2 in the Spatiotemporal Modeling

Appendix B. Sensitivity and Subgroup Analyses for Term Low Birth Weight

Appendix C. Sensitivity and Subgroup Analyses for Preterm Birth

Appendix D. Sensitivity and Subgroup Analyses for Preeclampsia

Appendix E. Sensitivity and Subgroup Analyses for Gestational Diabetes Mellitus

ABOUT THE AUTHORS

Jun Wu received her Ph.D. in environmental health sciences from the University of California–Los Angeles in 2004. Wu is currently associate professor of Public Health at the University of California–Irvine. She is also affiliated with the Center of Occupational and Environmental Health and the Department of Epidemiology at UC–Irvine. Her research interests are primarily in the fields of air pollution exposure assessment and air pollution epidemiology.

Olivier Laurent received his Ph.D. in environmental epidemiology from Rennes 1 University, France in 2007. From 2012 to 2014, Laurent was a postdoctoral researcher with the Program in Public Health at UC–Irvine. He currently works as a researcher at the French Institute for Radiation Protection and Nuclear Safety (Institut de Radioprotection et de Sûreté Nucléaire).

Lianfa (Leo) Li received his Ph.D. in geographical information science from Chinese Academy of Sciences in 2005. From 2010 to 2014, he was a postdoctoral researcher with the Program in Public Health at UC–Irvine. He currently works as a research associate at the Department of Preventive Medicine, University of Southern California.

Jianlin Hu received his Ph.D. in atmospheric sciences from the University of California–Davis in 2012. He currently works as a postdoctoral researcher in the Department of Civil and Environmental Engineering, UC–Davis. He also works for the Nanjing University of Information Science and Technology in China.

Michael Kleeman received his Ph.D. in environmental engineering science from California Institute of Technology in 1998. He is currently a professor in the Department of Civil and Environmental Engineering, UC–Davis.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Haghighat N, Hu M, Laurent O, Chung J, Nguyen P, Wu J. 2016. Comparison of birth certificates and hospital-based birth data on pregnancy complications in Los Angeles, California. BMC Pregnancy and Childbirth 16:93; doi:10.1186/s12884-016-0885-0.

Laurent O, Hu J, Li L, Kleeman M, Bartell SM, Cockburn M, et al. 2016. A statewide nested case–control study of preterm birth and air pollution by source and composition: California, 2001–2008. Environ Health Perspect; Available: *http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2016/2/ehp.1510133.acco.pdf*. [advance publication 19 February 2016].

Laurent O, Hu J, Li L, Kleeman M, Bartell S, Escobedo L, et al. 2016. Low birth weight and air pollution in California: Which sources and components drive the risk? Environ Int 92–93:471–477.

Li L, Laurent O, Wu J. 2016. Spatial variability of the effect of air pollution on term birth weight: evaluating influential factors using Bayesian hierarchical models. Environmental Health 15:14; doi:10.1186/s12940-016-0112-5.

Young C, Laurent O, Chung J, Wu J. 2016. Geographic distribution of healthy resources and adverse pregnancy outcomes. Matern Child Health J; doi:10.1007/s10995-016-1966-4.

Beltran A, Wu J, Laurent O. 2014. Associations of meteorology with adverse pregnancy outcomes: a systematic review of preeclampsia, preterm birth and birth weight. Int J Environ Res Public Health 11:91–172.

Laurent O, Hu J, Li L, Cockburn M, Escobedo L, Kleeman M, et al. 2014. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ Res 134:488–95.

Laurent O, Wu J, Li L, Chung J, Bartell S. 2013. Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ Health 12:18.

Laurent O, Wu J, Li L, Milesi C. 2013. Green spaces and pregnancy outcomes in Southern California. Health & Place 24:190–195.

Li L, Wu J, Ghosh J, Ritz B. 2013. Estimating spatiotemporal variability of ambient air pollutant concentrations with a hierarchical model. Atmos Environ 71:54–63.

Li L, Wu J, Wilhelm M, Ritz B. 2012. Use of generalized additive models and cokriging of spatial residuals to improve land-use regression estimates of nitrogen oxides in Southern California. Atmos Environ 55:220–228.

ABBREVIATIONS AND OTHER TERMS

AADT	annual average daily traffic
AIRS	Aerometric Information Retrieval System
BMI	body mass index
CALINE4	CAlifornia LINE Source Dispersion Model Version 4
Caltrans	California Department of Transportation
CI	confidence interval
CMB	chemical mass balance
CO	carbon monoxide
EBK	empirical Bayesian kriging
EC	elemental carbon
EPA	U.S. Environmental Protection Agency
FINN	Fire Inventory from National Center for Atmospheric Research
FRC	functional road class
GAM	generalized additive model
GAMM	generalized additive mixed model
GC–MS	gas chromatography–mass spectrometry
GDM	gestational diabetes mellitus
GIS	geographic information system
IQR	interquartile range
LBW	low birth weight
MFB	mean fractional bias
MFE	mean fractional error
NDVI	normalized difference vegetation index
NIEHS	National Institute of Environmental Health Sciences
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
NPACT	National Particle Component Toxicity initiative
O_3	ozone
OC	organic carbon
OR	odds ratio
PAHs	polycyclic aromatic hydrocarbons
PAS	photoelectric aerosol sensor
PeMS	(California Department of Transportation) Performance Measurement System
PM	particulate matter
$PM_{0.1}$	particulate matter ≤ 0.1 µm in aerodynamic diameter (ultrafine particles)
$PM_{2.5}$	particulate matter ≤ 2.5 µm in aerodynamic diameter
POA	primary organic aerosols
pPAH	particle-bound polycyclic aromatic hydrocarbon
PTB	preterm birth
RMSE	root mean square error
SAPRC	Statewide Air Pollution Research Center
SCAG	Southern California Association of Governments
SES	socioeconomic status
SOA	secondary organic aerosols
UCD/CIT	University of California–Davis/California Institute of Technology
UCD_P	primary chemical transport model developed by UCD
UFPs	ultrafine particles (aerodynamic diameter ≤ 0.1 µm)
WRF	Weather Research and Forecasting

CRITIQUE
Health Review Committee

HEI

Research Report 188, *Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women*, J. Wu et al.

INTRODUCTION

There is growing epidemiologic evidence of associations between maternal exposure to ambient air pollution and a range of adverse birth outcomes, including low birth weight (LBW*) and preterm birth (PTB) (Pedersen et al. 2013; Stieb et al. 2012; Vrijheid et al. 2011). A few studies have also recently reported that exposure to ambient air pollution may also increase the risk of some common pregnancy complications (see textbox), such as preeclampsia, gestational hypertension, or gestational diabetes mellitus (GDM) (Eze et al. 2015; Pedersen et al. 2014). Adverse birth and pregnancy outcomes are important not only because of their immediate impacts on maternal and infant health, but also because of the subsequent health and developmental consequences through the individual's life course (e.g., in case of LBW and PTB) (Blumenshine et al. 2010).

Research findings, however, have been mixed. This could reflect genuine differences of effects across different study populations, locations, or specific pollutants and pollutant mixtures; methodologic differences in study designs or analysis methods; or random variation (Woodruff et al. 2009). For example, various studies assess air pollution exposure differently. Some studies have relied on routine ambient air pollution monitoring stations, which do not capture the fine-scale (within-city) exposure contrasts adequately. Consequently, these studies might introduce substantial exposure misclassification. Within-city studies using, for example, land-use regression models may capture spatial contrasts sufficiently, but may have limited temporal coverage, another important feature of studies of adverse pregnancy outcomes. Moreover, little is known about the effect of pollution exposure during certain stages of pregnancy, although some studies suggest that exposure during late pregnancy is associated with LBW (e.g., Rich et al. 2015). Often, the high correlation between trimester-specific exposures may hamper such analysis (e.g., Pedersen et al. 2013).

In response to Request for Applications No. 09-4, "Walter A. Rosenblith New Investigator Award," Dr. Jun Wu of the University of California–Irvine submitted an application for a three-year study, "Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate Matter Air Pollution in Pregnant Women." She proposed to identify the sources and components of air pollution mixtures that contribute most to adverse pregnancy outcomes. She also planned to investigate whether the health effects are modified by factors such as socioeconomic status (SES), education, and body mass index ("effect modification"). The HEI Research Committee recommended Dr. Wu's application for funding because there had been few studies of air pollution and adverse birth and pregnancy outcomes at that time and because of the potential to disentangle the respective role of several pollutants or air pollution mixtures.

Pregnancy Complications

Gestational hypertension, preeclampsia, and gestational diabetes mellitus are fairly common complications of pregnancy. *Gestational hypertension*, or pregnancy-induced hypertension, is the development of hypertension in a pregnant woman after 20 weeks of gestation without the presence of protein in the urine or other signs of preeclampsia. *Hypertension* is defined as having a blood pressure greater than 140/90 mm Hg. *Preeclampsia* is a hypertensive syndrome specific to pregnancy, defined as new hypertension and substantial protein in the urine: if not treated, it can have serious—even fatal—consequences. Gestational diabetes mellitus is defined as intolerance to glucose that is first diagnosed or has its onset during pregnancy.

Dr. Jun Wu's 3-year study, "Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate Matter Air Pollution in Pregnant Women," began in February 2011. Total expenditures were $461,870. The draft Investigators' Report from Wu and colleagues was received for review in November 2014. A revised report, received in August 2015, was accepted for publication in October 2015. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Critique.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Critique is intended to aid the sponsors of HEI and the public by highlighting both the strengths and the limitations of the study and by placing the Investigators' Report into scientific and regulatory perspective.

APPROACH

The specific aims of the study were twofold:

1. To determine how exposure to local traffic-related air pollution (including polycyclic aromatic hydrocarbons [PAHs] and NO_2 in a subset) and to ambient concentrations of primary organic aerosols, secondary organic aerosols, and trace metals in PM (particulate matter) affects the risks of adverse birth and pregnancy outcomes in California women.
2. To examine the effect modification in California women by factors such as SES, smoking, body mass index, gestational weight gain, diabetes, and hypertension for PTB and LBW.

The investigators conducted a retrospective nested case–control study using birth certificate data from a source population of about 4.4 million birth records in California from 2001 to 2008. They analyzed data on LBW at term (infants born between 37 and 43 weeks of gestation and weighing less than 2500 g), PTB (infants born before 37 weeks of gestation), and preeclampsia (including eclampsia) of the mother during the pregnancy. In addition, they obtained data on GDM for the years 2006–2008. In the analyses, all outcomes were included as binary variables.

Maternal residential addresses at the time of delivery were geocoded, and a large suite of air pollution exposure metrics was considered: (1) regulatory monitoring data on concentrations of criteria pollutants NO_2, $PM_{2.5}$ (particulate matter ≤ 2.5 µm in aerodynamic diameter), and O_3 estimated by empirical Bayesian kriging; (2) concentrations of primary and secondary $PM_{2.5}$ and $PM_{0.1}$ components and sources estimated by the University of California–Davis Chemical Transport Model; (3) traffic-related ultrafine particles (UFPs) and concentrations of carbon monoxide (CO) and nitrogen oxides (NO_x) estimated by a modified CALINE4 air pollution dispersion model; and (4) proximity to busy roads, road length, and traffic density calculated for six different buffer sizes (< 50 m to 300 m) using geographic information system (GIS) tools. In addition, the following additional exposure metrics were considered in Los Angeles County only: (1) concentrations of PAHs estimated using a spatial mixed regression model with research monitoring data and (2) concentrations of NO_2 estimated by a spatiotemporal prediction model with research and regulatory monitoring data. The PAHs model was built using two 1-week measurements in the winter (36 sites) and two 1-week measurements in the summer (39 sites) of 2009. The NO_2 model was built using measurements at about 240 sites in the large metropolitan Los Angeles area in the period 2000–2009. In total, 50 different exposure metrics were available for the analyses. The exposure of primary interest was the mean of the entire pregnancy period for each mother, although analyses using trimester-specific means are presented in an appendix as well.

For the health analyses, controls were randomly selected from the source population. PTB controls were matched on conception year. Note that for the PTB controls, exposure estimates were truncated at the gestational age reached by the PTB case to which the control had been matched.

Term LBW, preeclampsia, and GDM were analyzed using generalized additive mixed models with inclusion of a random effect per hospital. PTB analyses were conducted using conditional logistic regression, with no adjustment for hospital.

The main results were adjusted for race and education as categorical variables and were adjusted for maternal age and median household income at the census-block level. The influence of important other potential confounders or effect modifiers (e.g., maternal smoking) was investigated in sensitivity and subgroup analyses; the results are presented in the appendix to the Investigators' Report. Results were expressed as odds ratios per interquartile range increase of exposure (for the pollutants) or per fixed unit increment (for the road traffic indicators).

The investigators mostly performed single-pollutant analyses, apart from a few two-pollutant models that included $PM_{2.5}$ with other pollutants that were run for one of the outcomes, PTB.

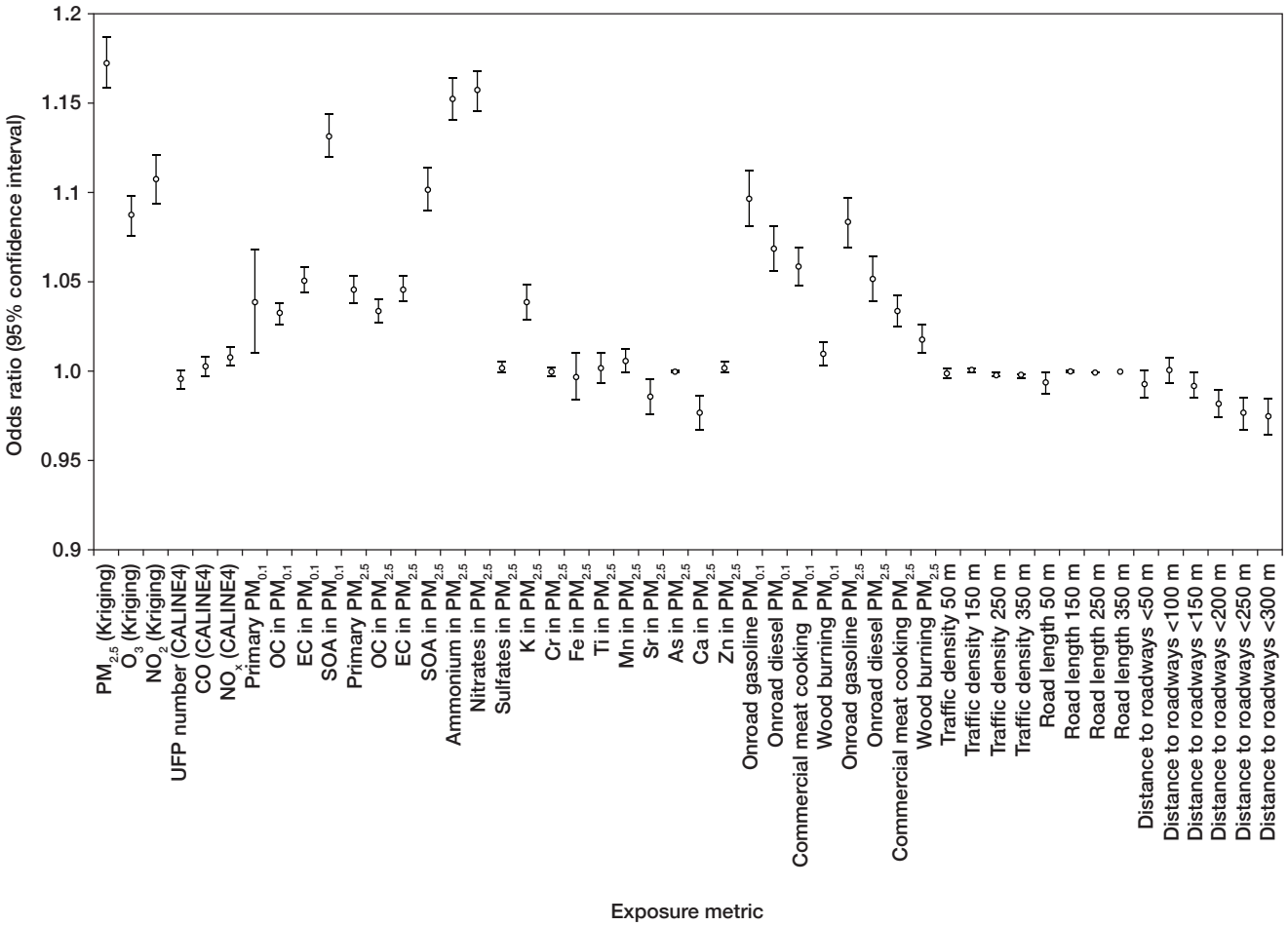
SUMMARY OF RESULTS

- An increase of various air pollution metrics was associated with an increased risk of PTB (Critique Figure 1). The strongest association was reported for $PM_{2.5}$ mass (estimated using kriging). In addition, associations were reported for some primary and secondary PM components/sources (e.g., those related to traffic, meat cooking, wood burning, ammonium, and nitrates) and for NO_2 and O_3. Particulate ammonium and nitrate associations were most robust after adjusting for $PM_{2.5}$ mass.

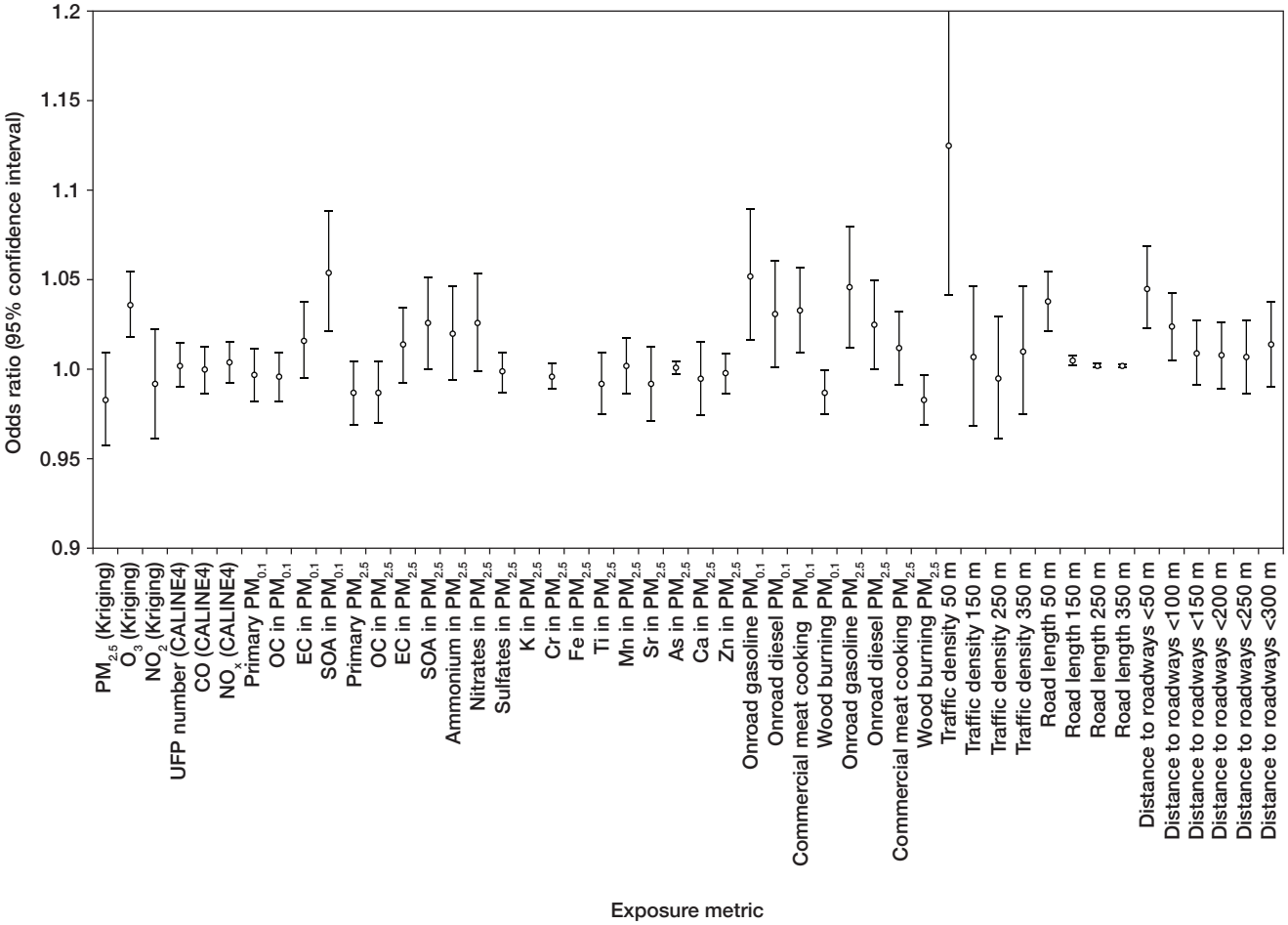
- The study identified several factors, most notably race and household income, that modify the reported PTB associations. Typically, associations were stronger for African American and Hispanic women and for households with low income.
- The evidence for an increased risk of term LBW with an increase in air pollution was weaker overall (Critique Figure 2). Moreover, decreases of many air pollution metrics were associated with an increased risk of preeclampsia (Critique Figure 3) and GDM (not shown). Note that GDM was only available for 3 years of the 8-year study period.
- Typically, measures of proximity to busy roads, road length, and traffic density were not (or were inversely) associated with the adverse birth and pregnancy outcomes. Only a few road traffic indicators in the 50 and 100 m buffers were associated with an increased risk of term LBW. Positive associations were also observed with PTB when the analyses were restricted to the small subset of births with the best geocoding accuracy.

HEALTH REVIEW COMMITTEE EVALUATION

In its independent review of the study, the HEI Health Review Committee concluded that Wu and colleagues had conducted a comprehensive nested case–control study of air pollution and adverse birth and pregnancy outcomes. The Committee thought that the study was generally well conducted, with thorough analyses. The Committee noted



Critique Figure 1. Associations between PTB and air pollution in California.

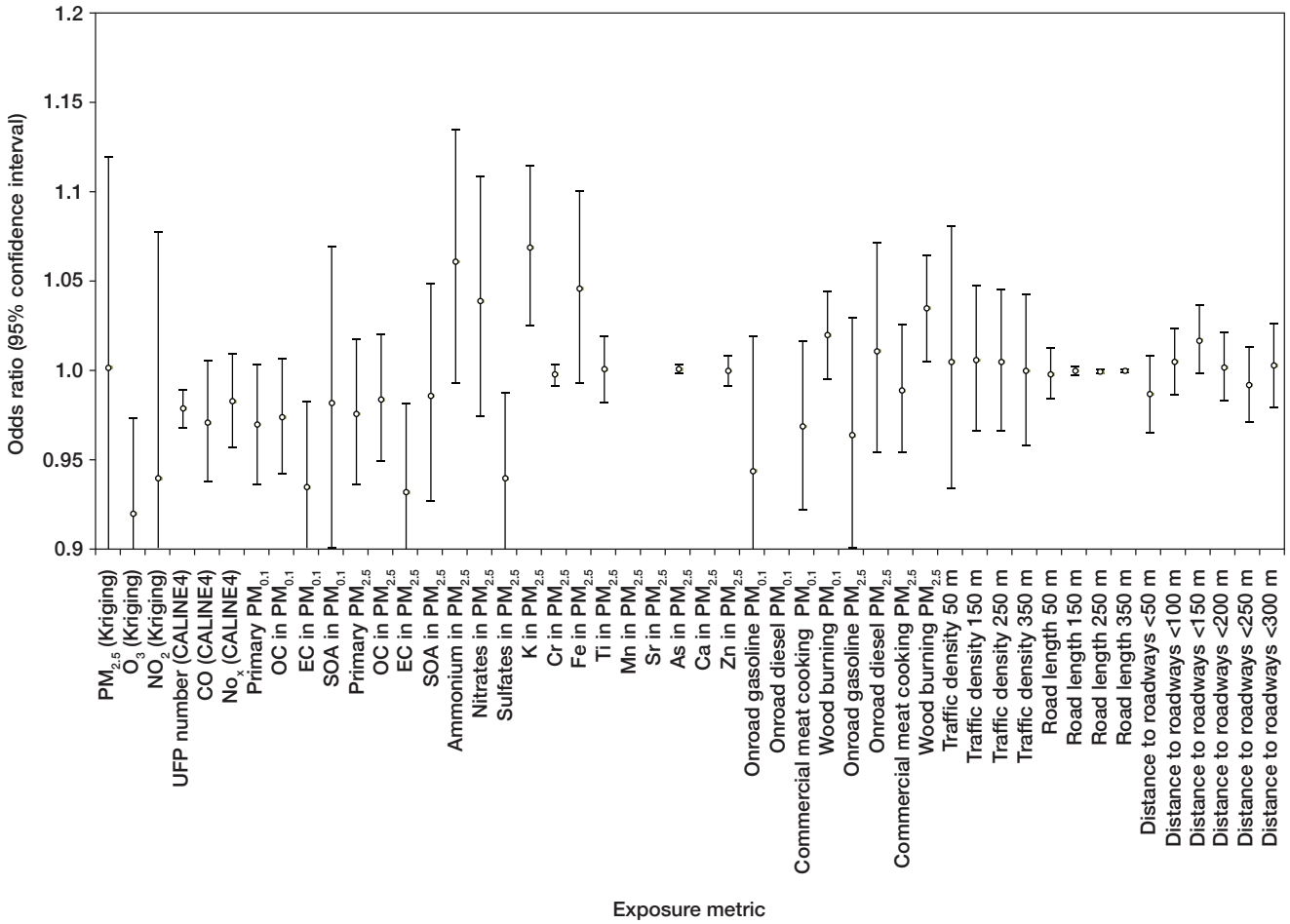


Critique Figure 2. Associations between term LBW and air pollution in California.

two major strengths of the study: the very large data set with a source population of about 4.4 million birth records in California from 2001 to 2008, and the extensive exposure assessment, estimating residential exposure for a large suite of air pollution exposure metrics using a variety of state-of-the-art methods and models. They also noted that the report was well written and well organized. The Committee considered Dr. Wu an exceptional recipient of HEI's Walter A. Rosenblith New Investigators Award, and they were impressed by her performance and successful completion of an ambitious project. The Committee also noted the impressive list of publications resulting from this research. The study by Wu and colleagues documented associations between increases in various air pollution metrics and increased risks of PTB. The exposure of the PTB controls was truncated at the same gestational age as that of the PTB case to which the control was matched, which is an advance over some past studies. This approach could help eliminate possible bias caused by different lengths of pregnancy and, thus, different exposure periods (Lewis et al. 2011; Woodruff et al. 2009).

The evidence was weaker overall for term LBW, and, unexpectedly, decreases of many air pollution metrics were associated with an increased risk of preeclampsia and GDM. The Committee has summarized below some analytical issues that should be considered when interpreting the results.

Although the source population was very large, only a subset of controls was used, to reduce computational demands. Hence, some of the term LBW, preeclampsia, and GDM models did not converge, especially in the subgroup analyses, presumably because of a lack of data. The Committee thought that the lack of convergence may have been related to the inclusion of a random effect for hospital



Critique Figure 3. Associations between preeclampsia and air pollution in California.

in the models and that it would have been useful to explore the reasons for nonconvergence in more detail.

The investigators suggested that underreporting in the registry data, especially in low-SES groups, might have caused the many negative associations found for preeclampsia and GDM, but the Committee thought this explanation could be explored further. Although some underreporting is to be expected for preeclampsia and GDM, especially compared with objective measures such as term LBW, in general, the study findings contradict most previous studies showing positive associations of different air pollution indicators with preeclampsia and GDM, without mentioning large underreporting issues (Eze et al. 2015; Pedersen et al. 2014). The investigators could have investigated this potential reason more directly by rerunning the analyses in the subpopulation for which both birth certificate data and hospital-based birth records were available. The investigators did use these data to examine differences in reporting between hospital records and birth certificate data and to determine if such differences vary by maternal SES indicators. In addition, they refer to their previous study (Wu et al. 2009, 2011), which does document positive associations between air pollution and preeclampsia using birth data from the same four hospitals, though these data were for the years 1997–2006.

There is always a trade-off between small studies with typically detailed information available at the individual level and large studies using routinely collected health databases with less detailed information, although an investigation could combine the best of both approaches by, for example, combining different smaller studies (e.g., Pedersen et al. 2013). The advantage of using birth registry data in a study is that it can cover very large, representative populations (in this case, the whole state of California).

A drawback, however, is that relatively little information may be available on important potential confounders and so the study may need indirect approaches to correct for important confounders (e.g., Shin et al. 2014). In the current study, maternal smoking was only recorded in the last two years of the study period, and no data were available regarding passive smoking. In addition, the authors discussed some auxiliary data to tackle possible underreporting of smoking among pregnant women. Those are all appropriate approaches in the absence of such data at the individual level. However, the absence of information on potential confounders at the individual level is only partly addressed in the current study.

Exposure measurement error is a potential source of bias in all epidemiologic studies (e.g., Sheppard et al. 2012). All exposure methods and modeling techniques to estimate exposures at the residential level provide, at best, an approximation of individual exposure. Residential mobility—a potentially important source of error in exposure predictions—was not taken into account in the exposure assessment. The impact of exposure measurement error on health effect estimations can be substantial, potentially distorting associations, reducing the power to detect effects, and leading to invalid inferences. Exposure measurement error may differ between components or sources; typically, $PM_{2.5}$ mass is estimated with better accuracy and precision than its components or its specific sources (Bell et al. 2011; Thurston et al. 2011). This is because $PM_{2.5}$ levels tend to be more uniform across large areas than pollutants such as NO_2 and several PM components such as elemental carbon, which exhibit higher spatial variation. Therefore, the empirical Bayesian kriging approach used by Wu and colleagues to estimate $PM_{2.5}$, NO_2, and O_3 may be more appropriate for a pollutant such as $PM_{2.5}$ than for NO_2 because this approach lacks the level of detail needed to capture small-scale spatial variations of air pollution. Similarly, the chemical transport models used by Wu and her study team computed pollutant concentrations from approximately 900 sources of primary particles in California at 4 km × 4 km grid resolution. These models capture regional large-scale air pollution patterns, with the best model performance for $PM_{2.5}$ relative to specific particle components and sources. (See, for example, Figure 1 in the Investigators' Report. Note in particular the large uncertainty in the modeling of sulfate.)

Land-use regression models, in contrast, focus primarily on high-resolution spatial variability in air pollutant concentrations, but they require a dense monitoring network, which, in the present study, was only available for NO_2 in the Los Angeles area. The PAHs land-use regression models were built with only approximately 40 sites, compared with approximately 240 sites for NO_2. The limited number of sites for PAH models may not be sufficient in Los Angeles, a large city characterized by generally high levels of air pollution and high spatial contrasts within the city. The CALINE4 air dispersion model accounted for spatiotemporal differences in pollution concentrations, but relies on assumptions that dispersion patterns are Gaussian, an assumption that may not be valid. Also very important, CALINE4 relies on the quality of model input variables such as traffic counts and emission factors (HEI Panel on the Health Effects of Traffic-Related Air Pollution 2010).

In the current study, measures of proximity to busy roads, road length, and traffic density were assessed as well, but they were typically not (or inversely) associated with the adverse birth and pregnancy outcomes. Only a few road traffic indicators in the 50 and 100 m buffers were associated with an increased risk of term LBW. The Committee found this puzzling, because those measures are typically straightforward, precise, directly relevant to land-use patterns, and easy to assess and apply. The investigators describe "poor geocoding" as a potential explanation and showed, for example, positive associations with PTB when analyses were restricted to the small subset of births with the best geocoding accuracy (15% of the PTB cases) (Appendix Table C.2). However, the Committee questioned this explanation, because any errors in geocoding would likely behave as random errors, thus not distorting associations. In general, the Committee thought that the analysis of road traffic indicators in the 50 m buffer was hampered by the lack of contrast, and the results are therefore difficult to interpret (Appendix Table A.3, showing a median of 0 for those variables). Also, when investigating so many exposure metrics and outcomes, researchers must look for consistency in effects rather than highlighting isolated positive associations, because a few false associations are to be expected.

Most of the results in the report were based on analyses using single-pollutant models, which is a reasonable approach but ignores that people are exposed to complex mixtures of pollutants. The investigators conducted a few two-pollutant models for PTB (Appendix Tables C.13 and C.14) at the suggestion of the HEI Review Committee, but the investigators interpreted them too cautiously, according to the Committee.

The Committee thought that the few two-pollutant models that were run provided important insights. The strongest positive association was reported for $PM_{2.5}$ mass and PTB in both single- and two-pollutant models. In addition, most components and source-specific

positive associations disappeared after adjusting for $PM_{2.5}$ mass. Consequently, the Committee believed that the study did not provide any conclusive evidence of the specific health impacts of individual PM components or sources. Only particulate ammonium and nitrate associations were robust after adjusting for $PM_{2.5}$ mass. Both ammonium and nitrate are secondary inorganic aerosols, representing largely agriculture emissions (ammonium) and combustion sources (nitrate).

Future studies should consider multipollutant models; air pollution epidemiology is increasingly moving toward analysis of mixtures and multipollutant modeling (Dominici et al. 2010). Advanced statistical methods are being developed to investigate the health effects of air pollution mixtures (e.g., Coull et al. 2015; Molitor et al. 2016), although it remains a challenging area of research. The current study created a new data set to which such novel methods could be applied.

Over the past two decades, much work has been devoted to the identification of specific particle components and sources that might be more or less harmful than others. For example, HEI's National Particle Component Initiative (NPACT) found that no component or source of $PM_{2.5}$ can so far be eliminated (Lippmann et al. 2013; Vedal et al. 2013). A similar conclusion was drawn by Stanek and colleagues (2011) in a review of earlier published studies on the same topic. The current study adds to this important ongoing debate.

SUMMARY AND CONCLUSION

Wu and colleagues have conducted a comprehensive nested case–control study of air pollution and adverse pregnancy and birth outcomes. The very large data set and the extensive exposure assessment were strengths of the study. The study documented associations between increases in various air pollution metrics and increased risks of PTB, whereas for the other outcomes (term LBW), the evidence was weaker overall, and decreases of many air pollution metrics were associated with an increased risk of preeclampsia and GDM. The HEI Health Review Committee concluded that the study was generally well conducted, with thorough analyses, although the Committee identified some analytical issues that should be considered when interpreting the results. For example, some models did not converge, and there was underreporting listed for preeclampsia and GDM in the registry data, especially in lower-SES groups; the Committee believed that those issues were not fully explored. In addition, poor geocoding and the lack of contrast hampered interpretation of road traffic indicators in the smallest buffer (< 50 m), and most results were based on single-pollutant models. The few two-pollutant models that were run for PTB provided important insights, showing the strongest association for $PM_{2.5}$ mass, while components and source-specific positive associations largely disappeared after adjusting for $PM_{2.5}$ mass. This study adds to the ongoing debate about whether some particle components and sources are of greater public health concern than others.

ACKNOWLEDGMENTS

The Health Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Sumi Mehta and Aaron Cohen for their oversight of the study, to Hanna Boogaard for her assistance in preparing its Critique, to Patricia Boyd for science editing of this Report and its Critique, and to Fred Howe, Jason Miranda, Hope Green, and Hilary Selby Polk for their roles in preparing this Research Report for publication.

REFERENCES

Bell ML, Ebisu K, Peng RD. 2011. Community-level spatial heterogeneity of chemical constituent levels of fine particulates and implications for epidemiological research. J Expo Sci Environ Epidemiol 21:372–384.

Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. 2010. Socioeconomic disparities in adverse birth outcomes: a systematic review. Am J Prev Med 39:263–272.

Coull BA, Bobb JF, Wellenius GA, Kioumourtzoglou M-A, Mittleman MA, Koutrakis P, et al. 2015. Part 1. Statistical Learning Methods for the Effects of Multiple Air Pollution Constituents. In: Development of Statistical Methods for Multipollutant Research. Research Report 183. Boston, MA:Health Effects Institute.

Dominici F, Peng RD, Barr CD, Bell ML. 2010. Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. Epidemiology 21:187–194.

Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Künzli N, et al. 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ Health Perspect 123:381–389.

HEI Panel on the Health Effects of Traffic-Related Air Pollution. 2010. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. HEI Special Report 17. Boston, MA:Health Effects Institute.

Lewis C, Hoggatt KJ, Ritz B. 2011. The impact of different causal models on estimated effects of disinfection by-products on preterm birth. Environ Res 111:371–376.

Lippmann M, Chen LC, Gordon T, Ito K, Thurston GD. 2013. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components. Research Report 177. Boston, MA:Health Effects Institute.

Molitor J, Coker E, Jerrett M, Ritz B, Li A. 2016. Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes. In: Development of Statistical Methods for Multipollutant Research. Research Report 183. Boston, MA:Health Effects Institute.

Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F, et al. 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med 1:695–704.

Pedersen M, Stayner L, Slama R, Sörensen M, Figueras F, Nieuwenhuijsen MJ, et al. 2014. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. Hypertension 64:494–500.

Rich DQ, Liu K, Zhang J, Thurston SW, Stevens TP, Pan Y, et al. 2015. Differences in birth weight associated with the 2008 Beijing Olympics air pollution reduction: results from a natural experiment. Environ Health Perspect 123:880–887.

Sheppard L, Burnett RT, Szpiro AA, Kim SY, Jerrett M, Pope CA 3rd, et al. 2012. Confounding and exposure measurement error in air pollution epidemiology. Air Qual Atmos Health 5:203–216.

Shin HH, Cakmak S, Brion O, Villeneuve P, Turner MC, Goldberg MS, et al. 2014. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. Environ Res 134:482-487.

Stanek LW, Sacks JD, Dutton SJ, Dubois J-JB. 2011. Attributing health effects to apportioned components and sources of particulate matter: an evaluation of collective results. Atmos Environ 45:5655–5663.

Stieb DM, Chen L, Eshoul M, Judek S. 2012. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. Environ Res 117:100–111.

Thurston GD, Ito K, Lall R. 2011. A source apportionment of U.S. fine particulate matter air pollution. Atmos Environ 45:3924–3936.

Vedal S, Campen MJ, McDonald JD, Kaufman JD, Larson TV, Sampson PD, et al. 2013. National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects. Research Report 178. Boston, MA:Health Effects Institute.

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, et al. 2011. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect 119:598–606.

Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. 2009. Methodological issues in studies of air pollution and reproductive health. Environ Res 109:311–320.

Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. 2009. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast Air Basin of California. Environ Health Perspect 117:1773–1779.

Wu J, Wilhelm M, Chung J, Ritz B. 2011. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res 111:685–692.

RELATED HEI PUBLICATIONS: MULTIPOLLUTANTS, BIRTH OUTCOMES, AND METHODS

Number	Title	Principal Investigator	Date
Research Reports			
189	Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China	Z. Qian	In Press
183	Development of Statistical Methods for Multipollutant Research		
	Part 1. Statistical Learning Methods for the Effects of Multiple Air Pollution Constituents	B.A. Coull	2015
	Part 2. Development of Enhanced Statistical Methods for Assessing Health Effects Associated with an Unknown Number of Major Sources of Multiple Air Pollutants	E.S. Park	2015
	Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes	J. Molitor	2016
179	Development and Application of an Aerosol Screening Model for Size-Resolved Urban Aerosols	C.O. Stanier	2014
178	National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects	S.Vedal	2013
177	National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components	M. Lippmann	2013
175	New Statistical Approaches to Semiparametric Regression with Application to Air Pollution Research	J.M. Robins	2013
161	Assessment of the Health Impacts of Particulate Matter Characteristics	M.L. Bell	2012
152	Evaluating Heterogeneity in Indoor and Outdoor Air Pollution Using Land-Use Regression and Constrained Factor Analysis	J.I. Levy	2010
140	Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality	D. Krewski	2009
139	Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study	B. Brunekreef	2009
HEI Special Reports			
17	Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects		2010
16	Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects		2007
HEI Perspectives			
3	Understanding the Health Effects of Ambient Ultrafine Particles		2013

Copies of these reports can be obtained from HEI. PDFs are available as free downloads at http://pubs.healtheffects.org.

HEI BOARD, COMMITTEES, and STAFF

Board of Directors

Health Research Committee

HEI BOARD, COMMITTEES, and STAFF

Health Review Committee

James A. Merchant, Chair *Professor and Founding Dean Emeritus, College of Public Health, University of Iowa*

Michael Brauer *Professor, School of Environmental Health, University of British Columbia, Canada*

Bert Brunekreef *Professor of Environmental Epidemiology, Institute of Risk Assessment Sciences, University of Utrecht, the Netherlands*

Mark W. Frampton *Professor of Medicine and Environmental Medicine, University of Rochester Medical Center*

Jana B. Milford *Professor, Department of Mechanical Engineering and Environmental Engineering Program, University of Colorado–Boulder*

Jennifer Peel *Professor of Epidemiology, Colorado School of Public Health and Department of Environmental and Radiological Health Sciences, Colorado State University*

Roger D. Peng *Professor of Biostatistics, Johns Hopkins Bloomberg School of Public Health*

Lianne Sheppard *Professor of Biostatistics, School of Public Health, University of Washington–Seattle*

Officers and Staff

Daniel S. Greenbaum *President*
Robert M. O'Keefe *Vice President*
Rashid Shaikh *Director of Science*
Jacqueline C. Rutledge *Director of Finance and Administration*
April Rieger *Corporate Secretary*

Hanna Boogaard *Staff Scientist*
Aaron J. Cohen *Consulting Scientist*
Maria G. Costantini *Principal Scientist*
Philip J. DeMarco *Compliance Manager*
Hope Green *Publications Associate*
Kathryn Liziewski *Research Assistant*
Anny Luu *Executive Assistant*
Heather Martin *Science Administration Assistant*
Hilary Selby Polk *Managing Editor*
Robert A. Shavers *Operations Manager*
Tyler Trainor *Staff Accountant*
Annemoon M.M. van Erp *Managing Scientist*
Donna J. Vorhees *Senior Scientist*
Katherine Walker *Senior Scientist*

HEALTH
EFFECTS
INSTITUTE

75 Federal Street, Suite 1400
Boston, MA 02110, USA
+1-617-488-2300
www.healtheffects.org

RESEARCH
REPORT

Number 188
July 2016