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Low birth weight and air pollution in California: Which sources and components drive the risk?

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Abstract

Introduction: Intrauterine growth restriction has been associated with exposure to air pollution, but there is a need to clarify which sources and components are most likely responsible. This study investigated the associations between low birth weight (LBW, <2500 g) in term born infants (37 gestational weeks) and air pollution by source and composition in California, over the period 2001–2008.

Methods: Complementary exposure models were used: an empirical Bayesian kriging model for the interpolation of ambient pollutant measurements, a source-oriented chemical transport model (using California emission inventories) that estimated fine and ultrafine particulate matter ($PM_{2.5}$ and $PM_{0.1}$, respectively) mass concentrations (4 km $\times$ 4 km) by source and composition, a line-source roadway dispersion model at fine resolution, and traffic index estimates. Birth weight was obtained from California birth certificate records. A case-cohort design was used. Five controls per term LBW case were randomly selected (without covariate matching or stratification) from among term births. The resulting datasets were analyzed by logistic regression with a random effect by hospital, using generalized additive mixed models adjusted for race/ethnicity, education, maternal age and household income.

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Results: In total 72,632 singleton term LBW cases were included. Term LBW was positively and significantly associated with interpolated measurements of ozone but not total fine PM or nitrogen dioxide. No significant association was observed between term LBW and primary PM from all sources grouped together. A positive significant association was observed for secondary organic aerosols. Exposure to elemental carbon (EC), nitrates and ammonium were also positively and significantly associated with term LBW, but only for exposure during the third trimester of pregnancy. Significant positive associations were observed between term LBW risk and primary PM emitted by on-road gasoline and diesel or by commercial meat cooking sources. Primary PM from wood burning was inversely associated with term LBW. Significant positive associations were also observed between term LBW and ultrafine particle numbers modeled with the line-source roadway dispersion model, traffic density and proximity to roadways.

Discussion: This large study based on complementary exposure metrics suggests that not only primary pollution sources (traffic and commercial meat cooking) but also EC and secondary pollutants are risk factors for term LBW.

1. Introduction

Intrauterine growth restriction has been associated with both short and long term adverse health effects, including increased risk of metabolic syndrome, systolic hypertension, obesity, type 2 diabetes mellitus and cardiovascular diseases (Chernausek, 2012; Salam et al., 2014). Results from several epidemiological studies suggest that exposure of pregnant women to air pollution results in higher risks of low birth weight (LBW, <2500 g) in term born infants, which is a marker for intrauterine growth restriction (Dadvand et al., 2013; Pedersen et al., 2013; Stieb et al., 2012, 2015). However, the sources and components of air pollution most likely to be responsible for the observed associations still need to be clearly identified.

Recent publications have suggested a possible influence of primary emissions from traffic on birth weight (e.g.: Lakshmanan et al., 2015; Laurent et al., 2013a, 2014; Malmqvist et al., 2011; Padula et al., 2012). The combustion of coal and biomass in the home where the pregnant women lived during pregnancy was also found to be positively associated with term LBW (Amegah et al., 2014). However, the influence of other sources of air pollution has seldom been investigated (Laurent et al., 2014; Wilhelm et al., 2012).

Only a few studies investigated the relation between PM composition and birth weight (e.g.: Basu et al., 2014; Bell et al., 2010, 2012; Darrow et al., 2011; Ebisu and Bell, 2012; Laurent et al., 2014). In these studies, the PM components most frequently associated with term LBW were elemental carbon (EC) (Basu et al., 2014; Bell et al., 2010; Darrow et al., 2011; Ebisu and Bell, 2012; Laurent et al., 2014; Pedersen et al., 2013; Slama et al., 2007; Wilhelm et al., 2012), iron (Basu et al., 2014; Bell et al., 2010; Laurent et al., 2014), titanium (Bell et al., 2012; Ebisu and Bell, 2012; Laurent et al., 2014) and nickel (Basu et

al., 2014; Bell et al., 2010; Ebisu and Bell, 2012). All the aforementioned studies except one (Laurent et al., 2014) attributed measurements from nearby monitors to subjects (within buffers up to a few kilometers) as a proxy for exposure. However, such exposure assessment methods may generate exposure misclassification (Laurent et al., 2013a; Schlesinger et al., 2006). In addition, restricting study populations to subjects living nearby monitors may result in selection bias and leave only a limited number of health outcomes for analyses, notably for relatively rare events such as LBW in term born infants. This issue is especially critical for the study of PM components, since monitors allowing for the assessment of PM composition remain very sparse (Basu et al., 2014).

Chemical transport models (CTMs) can help overcome many of the aforementioned limitations. CTMs can predict the chemical composition of primary and secondary PM with reasonable temporal and spatial resolution, while keeping track of source information. This approach can apply to pollutants for which direct measurement data are sparse. CTMs allows covering large domains where monitoring stations are not available, therefore avoiding study population restrictions, related selection bias and loss of statistical power (Laurent et al., 2016). Although CTMs have seldom been used to investigate the association between term LBW and air pollution by source and composition (Laurent et al., 2014), a recent major modeling effort conducted in California over a vast domain and a long duration now make it possible (Hu et al., 2014a, 2014b, 2015).

This work aimed at studying the relationships between LBW in term born infants and air pollution by source and composition in California. For that purpose, it builds not only on recent efforts of spatiotemporal chemical transport modeling of both primary and secondary particles by source and composition, but also on more commonly used air pollution metrics such as interpolated measurement data, local traffic dispersion modeling, and traffic indices.

2. Methods

2.1. Air pollution metrics

The air pollution indicators used in this study have been extensively described in other papers (Benson, 1989; Hu et al., 2014a, 2014b, 2015; Laurent et al., 2013a, 2014; Wu et al., 2009) and recently summarized in an open access publication (Laurent et al., 2016). These indicators are briefly presented below.

2.1.1. Empirical Bayesian kriging of monitoring station measurements—
Measurements from monitoring stations throughout the state for years 2000–2008 were obtained from the California Air Resources Board for total $PM_{2.5}$, nitrogen dioxide (NO_2) and ozone (O_3). Hourly gaseous pollutant measurements were converted to daily means using a criterion of 75% data completeness at a 24-hour basis. Only data for the 10 am–6 pm time windows were used to calculate eight-hour daily means for O_3. Monthly averages for pollutants were then calculated for stations with >75% days of valid data in a month. These monthly averaged concentrations were spatially interpolated between stations using an empirical Bayesian kriging (EBK) model (Pilz and Spöck, 2007) implemented in ArcGIS 10.1 (ESRI, Redlands, CA). Pollutant surface predictions were generated for 200 m * 200 m grids.

2.1.2. Chemical transport modeling—The daily mass concentration of primary PM (PM emitted directly into the atmosphere) and of secondary PM (formed in the atmosphere from gas-phase precursors) were estimated at 4 km × 4 km spatial resolution across two domains covering 92% of the California population for the period of 2000–2008, using the University of California-Davis/California Institute of Technology (UCD/CIT) chemical transport model (Hu et al., 2015). In the present study, the simulated PM concentrations were calculated for two particle size fractions ($PM_{2.5}$ and $PM_{0.1}$). The UCD/CIT model includes a complete description of atmospheric transport, deposition, chemical reaction, and gas-particle transfer. This model provided mass concentration estimates for primary PM total mass and for several chemical species in PM (OC, EC, nitrates, sulfates, ammonium and secondary organic aerosols (SOA)).

In addition, the University of California Davis/CIT_Primary (UCD_P) chemical transport model was used across the same geographical domain for the period of 2000–2006 to predict the daily mass concentrations for further chemical species and for the total mass of primary PM broken down by source (Hu et al., 2014a, 2014b). The model simulated daily primary PM mass concentrations, also at a 4 km × 4 km grid resolution, from ~900 sources. Composition profiles were applied combined with the primary PM mass concentration results from the UCD_P model to estimate the concentrations of chemical species in primary PM. The mass, source, and composition of size-resolved PM were tracked during model calculations. We decided a priori to include in our analyses UCD_P estimates of sources and components of primary PM for which detailed validation results were available: onroad gasoline, onroad diesel, commercial meat cooking and wood burning (Hu et al., 2014a). Nine species of PM (potassium, chromium, iron, titanium, magnesium, strontium, arsenic, calcium and zinc) were selected, all with the correlation above 0.8 between modeled and measured monthly average concentrations (Hu et al., 2014b).

2.1.3. CALINE4 dispersion modeling for road sources—A modified version of CAlifornia LINE Source Dispersion Model Version 4 (CALINE4) (Benson, 1989; Wu et al., 2009) was used to predict ambient concentrations from local traffic emissions of CO, NO_x, and ultrafine particle number (UFP) up to 3 km from maternal residences. Model inputs included roadway geometry and traffic counts, emission factors, and meteorological parameters (wind direction, wind speed, temperature stability class, and mixing heights). CALINE4 predictions in this study did not incorporate background levels of pollutants, thus solely represents the contribution from local traffic emissions.

2.1.4. Traffic and distance to roadways—Traffic densities within circular buffers of different sizes centered on maternal homes were calculated based on 2002 annual average daily traffic counts (AADT) data from the California Department of Transportation (CALTRANS, 2012). To estimate traffic density, AADT on each road segment was weighted by the length of this same road segment within the buffer. These traffic densities for year 2002 were then scaled to other years by multiplying them by the ratio of total vehicle miles traveled in California for the given year to the total vehicle miles traveled in California for year 2002 (CALTRANS, 2013). U.S. major roads data based on TeleAtlas streets (ESRI, 2010) were used to calculate the distance from each maternal home to the nearest major

roadway (which could be a freeway, a highway or a major arterial, as defined by categories of Functional Road Classes (FRC) A0-A5).

2.2. Study population

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 engine (Goldberg et al., 2008), which geocoded births at the centroid of tax parcels whenever feasible. The parcel-level geocoding generally has higher spatial precision than the zip code or city level geocoding, and is important in studying the associations between term LBW and air pollution indicators showing important variation at small geographic scale (e.g.: within a few hundred meters such as primary emissions from traffic estimated with CALINE4, traffic density and distance to roads). In total, we had 54.02% of addresses geocoded within a parcel, in which 14.14% of all births were geocoded to the exact centroid of a parcel. The main reason for not matching to a parcel was the lack of underlying parcel data (for example, some counties do not make parcel data available for free, as a result these are not available in most geocoders). However, 95% of addresses which could not be matched to a parcel could be matched to a street segment (i.e. the block on which the residence occurs). In total, 1361 births had no usable coordinates at all and 7512 infants were born to women residing outside of California. After excluding these births and those who had State File Number information missing (n=8119, partially overlapping with births lacking usable coordinates or which occurred outside of California), we obtained 4,370,371 births.

Multiple births (n=132,369) were excluded as well as infants with recorded birth defects or unknown birth defects status (n=18,811 and n = 675 respectively). Birth with missing information for gestational age (n=196,247), estimated gestational age shorter than 121 or longer than 319 days (n= 2051 and n= 41,017 respectively), or implausible combinations of birth weight and gestational age (n = 17,026) (Alexander et al., 1996) were excluded from the main analyses. Further, infants born to mothers older than 60 (n=43) were excluded. Several exclusion criteria overlapped for certain births, leaving 3,972,594 births from the source population. Infants born preterm (n = 394,683) were excluded from the source population of 3,972,594 birth records and infants born after 308 days of gestation (44 weeks, n=43,203) were further excluded for consistency with other recent studies (Bell et al., 2010, 2012; Darrow et al., 2011; Ebisu and Bell, 2012). From the remaining source population of 3,534,708 term births records in the entire California (period 2001–2008), 72,632 LBW cases were identified and included in the study. Five controls (term born children weighting ≥ 2500 g at birth) per case were randomly selected from the source population of potential term birth controls.

2.3. Statistical methods

A case-cohort approach was employed to analyze the association between each air pollutant and term LBW. As part of the primary analyses, the resulting datasets were analyzed by logistic regression with random effect per hospital using generalized additive mixed models (GAMMs) in the 'mgcv' package of the R environment (version 3.0.1.). The hospital

resolution was chosen so that it would help minimize the potential for bias that might be due to various quality of variable recording between hospitals. We first explored the shapes of the relationships between air pollution indicators and term LBW using smoothing splines. We then examined air pollution indicators as linear terms in the models instead. Random effects were introduced for the slope measuring the effect of air pollution on term LBW risk, as well as for the intercept of the model. For air pollution indicators that represent ambient concentration of air pollutants (either modeled or measured), we reported related odds ratios (ORs) and 95% confidence intervals (95% CI) for term LBW for an inter-quartile range increase air pollutant concentrations (IQR), based on the fixed effect. Scaling to the IQR allowed for a more straightforward comparison of effect sizes between air pollution indicators of different natures. To facilitate the quantitative comparison of associations between term LBW and traffic density across buffers of different sizes, we scaled ORs for this indicator to an increase of 100,000 vehicles per day per meter. Distance to roadway was analyzed using dichotomous indicators for living or not living within certain distances from roads.

Risk factors for term LBW other than air pollution were identified from the literature and a causal diagram was drawn (see Appendix Fig. A) to identify the minimal set of potential confounders for adjustment (Greenland et al., 1999). Based on this causal diagram, our primary analyses we adjusted for maternal race/ethnicity and educational level, using categorical variables, and maternal age and median household income by Census Block Group (U.S. Census Bureau, 2004), using smoothing splines. As part of sensitivity analyses, we also examined the influence of adjusting for additional risk factors: temperature, time of conception or population density (all adjusted for smoothing splines), diabetes (pre-pregnancy and gestational combined), chronic hypertension, preeclampsia, parity and the trimester of pregnancy during which primary care began. We examined the effects of further adjustment for body mass index (BMI) at the beginning of pregnancy and smoking during pregnancy in the subset of infants born in 2007 and 2008, since these variables were not recorded on birth certificate during the previous years.

For time varying variables (i.e.: measurements interpolated with EBK, predictions from the UCD_P, UCD/CIT and CALINE4 models), we conducted our primary analyses for "average pregnancy exposures". We also explored the association between term LBW and exposure to air pollution during different trimesters of pregnancy. We explored the influence of geocoding accuracy by a separate analysis of the subgroup of births geocoded to a parcel or the exact centroid of a parcel (the highest quality geocoding). Last, we conducted sensitivity analyses by using generalized estimating equations (GEEs) in order to estimate marginal effects. For that purpose we used the 'geepack' package of the R environment (version 3.0.1.). For all models, inferences were based on statistical significance at the 5% level.

This study has been approved by the Institutional Review Board of the University of California, Irvine.

3. Results

In our study population, the risk of term LBW varied by maternal characteristics, diseases and neighborhood income level, consistent with previous studies (Table 1). Descriptive statistics for air pollution metrics are presented in Appendix Table A. The distributions of traffic density and distance to roads among study subjects are presented in more details in Appendix Tables B and C, respectively.

By using random effects, GAMMs allowed the associations between air pollution metrics and term LBW to vary across hospitals. The ORs for term LBW presented in Table 2 reflect the median associations between air pollution metrics and term LBW, which would be observed in a typical hospital of the study setting.

When exposure averaged on the entire pregnancy was considered, a significant positive association was observed between term LBW and EBK-interpolated measurements of O_3 (after adjustment for primary confounders) [OR per IQR in exposure: 1.035 (95% CI: 1.017–1.054)] but not total $PM_{2.5}$ or NO_2 (Table 2). No significant association was observed between term LBW and primary $PM_{2.5}$ or $PM_{0.1}$ from all sources grouped together, modeled by UCD_P at a 4 km * 4 km resolution. 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, model convergence could not be reached for iron and potassium. Positive and close to significance associations were observed for SOA and nitrates in $PM_{2.5}$.

When primary PM exposure modeled with UCD_P was broken down by sources, term LBW risk was positively and significantly associated with primary $PM_{2.5}$ and $PM_{0.1}$ emitted by onroad gasoline [OR per IQR in exposure for $PM_{0.1}$: 1.051 (95% CI: 1.015–1.089)], onroad diesel [OR per IQR in exposure for $PM_{0.1}$: 1.030 (95% CI: 1.000–1.060)] and commercial meat cooking sources [OR per IQR in exposure for $PM_{0.1}$: 1.032 (95% CI: 1.008–1.056)]. Associations per IQR were slightly weaker for the $PM_{2.5}$ than for the $PM_{0.1}$ fraction but still statistically significant. When primary PM from several sources were included in a same statistical model, the positive association between term LBW and PM from gasoline was the most robust to the adjustment for other sources (Appendix Table D). Although this association was not statistically significant anymore after adjusting for PM from commercial meat cooking, the effect size [OR per IQR in exposure for $PM_{0.1}$: 1.043 (95% CI: 0.995; 1.094)] remained similar to that observed in the single source analysis. Primary PM from wood burning (both in the $PM_{0.1}$ and the $PM_{2.5}$ fractions) was inversely and significantly associated with term LBW risk (Table 2), even after adjusting for PM from other sources (Appendix Table D). We acknowledge that since the correlations between primary PM from gasoline, diesel and meat cooking sources were high (between 0.70 and 0.95), the results of models including PM from several of these sources must be considered with caution. For the same reason, it was not attempted to put both primary $PM_{0.1}$ and the $PM_{2.5}$ from the same source in the same model.

When primary emissions from local traffic were modeled at a fine geographical resolution using CALINE4, no statistically significant association was observed between term LBW and UFP number, CO or NO_x in the entire population (Table 2). However, when analyses

were restricted to the population in which maternal addresses could be geocoded with the best accuracy (i.e. at the exact centroid of a parcel), all three pollutants were positively associated with term LBW (Appendix Table E). 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 traffic density [OR per 100,000 vehicles per day per meter: 1.124 (95% CI: 1.040; 1.214)] within 50 m from maternal homes (Table 2). Consistently, term LBW risk was significantly increased in women living within 50 m (OR: 1.044; 95% CI: 1.022; 1.068) and even 100 m (OR: 1.023; 95% CI: 1.004; 1.042) of a major roadway (defined as freeways, highways and major arterials). Odds ratios regularly decreased from 50 m to 250 m, although none was statistically significant beyond 100 m.

Adjusting for potential confounders other than maternal age, race, education and neighborhood socioeconomic status as part of sensitivity analyses generally had negligible impacts on results. However, adjusting for the time of conception had a noticeable impact on effect sizes, and sometimes on their direction (e.g.: for total $PM_{2.5}$ and NO_2). Nevertheless, adjustment for time of conception would not change the conclusions of the study, except that the association with diesel was not significant anymore whereas the positive association with nitrates in PM2.5 became statistically significant (Appendix Table F). Adjusting for temperature cancelled out the significant associations between term LBW and ozone, SOA in $PM_{2.5}$ or primary PM from wood burning but not the other pollutants (see Appendix Table G). After this additional adjustment, the positive association between nitrates in $PM_{2.5}$ and term LBW became statistically significant (Appendix Table G).

When exposures were averaged on each trimester of pregnancy, positive association were observed between term LBW and exposure to elemental carbon (EC), nitrates, as well as ammonium during the third trimester of pregnancy. For SOA, the associations were positive and significant only for the second trimester of pregnancy, whereas they were for the first and second trimester for O_3 (Appendix Table H). For primary PM broken down by sources, the strongest positive associations were observed between term LBW and exposure to primary PM from onroad gasoline, onroad and commercial meat cooking sources during the third trimester of pregnancy. No marked difference across trimesters was observed for CALINE4 estimates.

When sensitivity analyses were conducted by using GEEs (without random effects), the results overall were similar to those obtained by using GAMMs (e.g.: comparing results for exposure averaged on the entire pregnancy in Appendix Table I to those in Table 2). However, statistically significant positive associations were observed for more pollutants using GEE models than using GAMMs, including primary $PM_{0.1}$, primary $PM_{2.5}$, organic and elemental carbon in both fractions, ammonium, nitrates and sulfates in $PM_{2.5}$. The positive associations observed for primary PM from diesel, gasoline and commercial meat cooking were stronger from GEE models than those estimated using GAMMs (Appendix Table I). Estimates obtained for distance to roads using GEEs were unrealistically high or low, depending on the distance considered (data not shown). However our interpretations

have been focused on the results of GAMMs because these models allowed accounting for between-hospital variation in background risk and pollutant effects.

4. Discussion

This was a very large case-cohort study covering the entire California for a period of 8 years. Based on a wealth of air pollution metrics including modeled PM by source and composition, we observed consistent positive and significant associations between the risk of term LBW and indicators of primary traffic-related pollution. A significant positive association was also observed with primary PM from meat cooking, but this was less robust to alternative covariate adjustment strategies. Positive and significant associations with EC and with some secondary pollutants (nitrates, ammonium and SOA) were also observed. Depending on the pollutant, associations were strongest for exposures occurring during the second or third trimester of pregnancy.

A main strength of this study is the comprehensive air pollution exposure measures, especially as it benefits from an advanced chemical transport modeling effort (Hu et al., 2014a, 2014b, 2015). The strengths and limitations of these air pollution indicators and the discussion of their uses in air pollution and birth outcome studies have already been described in other papers (Benson, 1989; Hu et al., 2014a, 2014b, 2015; Laurent et al., 2013a, 2014, 2016; Wu et al., 2009).

The EBK-interpolated surface of measured ambient $PM_{2.5}$, NO_2 and O_3 was expected to minimize biases from assigning data from one single monitor to populations living farther away (Laurent et al., 2014) and allowed for the inclusion of almost all term births in California in our study. EBK has major advantages for large studies covering long time periods, such as minimal need for interactive modeling (Pilz and Spock, 2007). The main limitations of this technique include its inability to take into account additional information from covariates, contrarily to other methods such as land use regression or cokriging, and its impossibility to perform anisotropic corrections. We acknowledge that exploring other methods such as land use regression, cokriging and Bayesian maximum entropy would be of interest in the future (Adam-Poupart et al., 2014). However, satisfactory results were obtained for the EBK-interpolated monthly concentrations using the leave-one-out cross validation, with correlation coefficients of 0.74, 0.72 and 0.65 for O_3, NO_2 and total $PM_{2.5}$, respectively. Nevertheless, since the EBK method relied solely on measurement data from only 75–182 monitoring stations unevenly and sparsely distributed over the entire California, it was not capable to capture the small-scale spatial variations of ambient pollutant concentrations. In the present study, sensitivity analyses showed that using either an EBK or a nearest station approach to estimate air pollutant concentrations yielded similar estimates of associations between term LBW and ambient pollutant concentrations (see Appendix Table J).

Compared to the spatial interpolation approach, the chemical transport models were superior in capturing spatial variability in ambient concentrations, but inferior in capturing temporal variability. However, they cover pollutants for which measurement data are very scarce such as ultrafine PM mass (Hu et al., 2014a), chemical species in PM (Hu et al., 2014b, 2015),

and source-specific primary PM (Hu et al., 2014a). We decided to include the particles size fractions, chemical components, and sources in this study based on the validation results for UCD_P (Hu et al., 2014a, 2014b) and UCD_CIT (Hu et al., 2015), respectively. In this study, we only included four major sources of primary PM that passed validation checks (Hu et al., 2014b), which represent some of the most ubiquitous sources in the environment of urban and/or rural populations. Because of the significant underestimation in secondary PM mass, we did not use source information for secondary PM.

Similarly, we decided a priori to include only primary PM components for which correlations between modeled and measured monthly concentrations (both in $PM_{2.5}$, since measurements for most components were available only for that fraction) were >0.8 at 5 sites. Total $PM_{0.1}$ mass prediction also agreed well with measurements (R = 0.81)(Hu et al., 2014b), and thus was included in the analysis. For secondary species, we included organic carbon, nitrate, and ammonium; the modeled concentration of these species agreed reasonably well with measurements based on average concentrations over several months. Although the predicted sulfate concentrations were not satisfactory because of missing emission sources (Hu et al., 2015), sulfates were also included because they contribute considerably to total PM mass (Bell et al., 2007). We could not validate secondary organic aerosols (SOA) predictions due to the difficulty to differentiate the SOA fraction from total organic aerosol in the measurements. Therefore, results for sulfate and SOA must be interpreted with caution in our study.

Compared to EBK and chemical transport models, the line source dispersion model CALINE4 was the most capable to capture small-scale variations in primary traffic emissions (Benson, 1989; Laurent et al., 2013a; Wu et al., 2009). However, this simple Gaussian dispersion model did not consider complex atmospheric mechanisms of transport, deposition, chemical reaction, and gas-particle transformation. In addition, model inputs had limited temporal resolution (e.g. annual average traffic counts, estimated mixing height by season and time of day). As a result, the dispersion model had limited capability in predicting temporal variability. Nevertheless, the model performed reasonably well with an overall correlation of 0.75 between modeled concentration and daily average particle number concentrations (N=357 days) measured from another study at four monitoring sites in southern California (three in Los Angeles County and one in Riverside County) (Laurent et al. 2016). Compared to the CALINE4 predictions, traffic density and distance to roads are cruder indicators of local traffic emissions, but they were used to check for consistency of our study with numerous other studies that used similar indicators.

One of the main limitations of this study is that we relied on ambient rather than personal exposure of mothers during pregnancy due to the lack of time activity information in this large population. In addition, since residential history and work addresses were not available in birth certificate data, our air pollution exposure assessment solely relied on maternal home address at the time of delivery. These sources of non-differential exposure measurement error likely decrease the precision of the epidemiologic associations and induce bias towards the null hypothesis.

We observed a positive association between term LBW and O_3, which is consistent with previous studies conducted in California (Laurent et al., 2013a; Morello-Frosch et al., 2010; Salam et al., 2005). It may seem surprising that we did not observe any association between total $PM_{2.5}$ and low birth weight, since a recent meta-analysis (Dadvand et al., 2013) as well as a major pooled analysis of European cohorts (Pedersen et al., 2013), an analysis of a large World Health Organization database (Fleischer, 2014), and a recent large-scale Canadian study (Stieb et al., 2015) all reported positive associations for this pollutant. However, the composition of $PM_{2.5}$ is highly variable across time and space (Bell et al., 2007), which might explain some of heterogeneity of effects across settings.

Regarding PM components, we only observed significant positive associations with SOA, EC nitrates and ammonium (only for exposure during the last trimester of pregnancy for the last three components). The positive association with EC is consistent with most previous literature (Basu et al., 2014; Bell et al., 2010; Darrow et al., 2011; Ebisu and Bell, 2012; Laurent et al., 2014; Pedersen et al., 2013; Slama et al., 2007; Wilhelm et al., 2012). Only one of the two previous studies which investigated the association between term LBW and ammonium (Basu et al., 2014; Ebisu and Bell, 2012) reported a positive association (Basu et al., 2014) but in this study the association was not significant anymore after adjusting for potential confounders. No positive association with nitrates was observed in previous studies (Basu et al., 2014; Ebisu and Bell, 2012).

We did not observe any significant associations with metals, contrarily to other studies (Basu et al., 2014; Bell et al., 2010; Ebisu and Bell, 2012). All these other studies attributed measurement from speciation monitors to subjects living within certain distances from them as surrogates for exposures, whereas we used a chemical transport model. Despite obvious advantages of the chemical transport model approach to better capture the spatial variability in pollutant concentrations, it might have led to a less optimal capture of temporal variation in species concentrations because of the lack of temporal resolution of emission inventories or source profiles. This might be a partial explanation for the lack of associations observed between term LBW and metals in PM in our study. Unfortunately, our mixed models did not converge for a few pollutants including iron and potassium, and the possibility that these species are positively associated with term LBW in California cannot be excluded. Potassium was actually found to be associated with term LBW in one other study (Bell et al., 2012), and iron in three other studies (Basu et al., 2014; Bell et al., 2010; Laurent et al., 2014).

Analyses of PM by source revealed positive associations between term LBW and PM from diesel, gasoline and commercial meat cooking. These findings are supported by other studies for gasoline (Wilhelm et al., 2012), diesel (Slama et al., 2007; Wilhelm et al., 2012), traffic related $PM_{2.5}$ overall (Bell et al., 2010) and meat cooking (Choi and Perera, 2012; Laurent et al., 2014; Wilhelm et al., 2012). 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 when the highest geocoding accuracy was considered. Our findings are consistent with previous studies, both for traffic density and proximity to major roads (Laurent et al., 2013a; Malmqvist et al., 2011; Padula et al., 2012; Pedersen et al., 2013; Wilhelm and Ritz, 2003;

Zeka et al., 2008). Overall, the consistency of results both across air pollution indicators in our study and across different studies for similar indicators, provides convincing evidence for the influence of primary traffic related pollution on intrauterine growth restriction. Regarding commercial meat cooking, since the observed association was less robust to alternative adjustment strategies, more research is warranted to help clarify the possible influence of this source on term low birth weight.

We have no straightforward explanation to the inverse association we observed with wood burning, which is contrasted with findings from other studies (Boy et al., 2002; Thompson et al., 2011). This association was not significant anymore after adjusting for temperature, which might provide a partial explanation (see Appendix Table G). Other potential explanations might be specific factors contributing to a more beneficial environment in places where wood is widely used as a heating source. A sensitivity analysis adjusting for population density still found a statistically significant inverse association between term LBW and PM from wood burning (see Appendix Table K), which does not suggest a major role of living in a rural versus urban place in explaining this association. Alternatively, exposure to greenness which is only partly related to population density and rural/urban status and has been positively correlated with birth weight in recent publications (Dadvand et al., 2012), notably in Southern California (Laurent et al., 2013b), might be another potential source of explanation. Further studies are warranted to investigate jointly the impacts of greenness and PM from different sources on term LBW.

5. Conclusion

This large study based on complementary exposure metrics points to primary pollution sources such as traffic and possibly commercial meat cooking as risk factors for term LBW, although evidence is more limited for the latter source. This study also points to EC and to secondary pollutants (ozone, nitrates, ammonium and SOA) as risk factors for term LBW.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Risk of term low birth weight by maternal characteristics.

Population characteristic	Number of subjects	Odds ratio (95% confidence interval)
Maternal race/ethnicity		
African American	25,004	2.829 (2.740; 2.922)
Asian	53,525	1.866 (1.817; 1.917)
Hispanic	221,177	1.361 (1.333; 1.389)
Multiple/other	10,021	1.384 (1.309; 1.462)
Caucasian	121,174	1.00 (reference)
Missing	4891	
Maternal education		
Lower than 8th grade	44,475	1.268 (1.230; 1.307)
9th grade to High School	193,557	1.380 (1.351; 1.409)
College (<4 years)	86,203	1.163 (1.134; 1.193)
College (4 years)	100,717	1.00 (reference)
Missing	10,840	
Median annual income by census block group		
$30,933	108,408	1.386 (1.355; 1.418)
$30,938–$42,483	108,547	1.224 (1.196; 1.253)
$42,500–$60,179	108,645	1.123 (1.097; 1.150)
$60,185	108,742	1.00 (reference)
Missing	1450	
Maternal age		
<15	568	2.142 (1.778; 2.581)
15 to 19	42,297	1.651 (1.605; 1.699)
20 to 24	100,201	1.263 (1.234; 1.293)
25 to 29	114,540	1.070 (1.045; 1.095)
30 to 34	105,483	1.00 (reference)
35 to 39	58,065	1.076 (1.047; 1.107)
40 to 44	13,856	1.391 (1.329; 1.456)
45 to 49	716	1.823 (1.534; 2.167)
50 and over	66	2.016 (1.161; 3.501)
Chronic hypertension		
Yes	1746	2.618 (2.371; 2.891)
No	434,035	1.00 (reference)
Missing	11	
Diabetes		
Yes	12,340	1.055 (1.006; 1.106)
No	423,441	1.00 (reference)
Missing	11	
Preeclampsia		

Population characteristic	Number of subjects	Odds ratio (95% confidence interval)
Yes	9875	4.258 (4.089; 4.434)
No	425,913	1.00 (reference)
Missing	4	
Primary care		
None	1817	3.277 (2.980; 3.603)
After first trimester	59,744	1.264 (1.237; 1.293)
First trimester	371,231	1.00 (reference)
Missing	3000	
Parity		
Primiparous	179,829	1.533 (1.508; 1.557)
Multiparous	255,768	1.00 (reference)
Missing	195	
Smoking during pregnancy (2007–2008 data only)		
Yes	3022	1.899 (1.75; 2.062)
No	110,353	1.00 (reference)
Pre-pregnancy body mass index (2007–2008 data only)		
19.9	13,452	1.917 (1.795; 2.048)
20–24.9	43,415	1.203 (1.135; 1.275)
25–29.9	25,656	1.062 (0.997; 1.131)
30–34.9	11,809	1.00 (reference)
>35	7311	1.074 (0.988; 1.167)
Missing	11,732	

Table 2

Associations between term low birth weight and air pollution in California[a].

Air pollution indicator	Number of cases	IQR[b]	Odds ratio (95% confidence interval)[c]	p value
Measured pollutant concentrations interpolated by empirical Bayesian kriging				
$PM_{2.5}$	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		No convergence	
Cr in $PM_{2.5}$	48,541	0.002	0.995 (0.988; 1.003)	0.20
Fe in $PM_{2.5}$	48,541		No convergence	
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 sources*				
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

Air pollution indicator	Number of cases	IQR[b]	Odds ratio (95% confidence interval)[c]	p value
CALINE4 modeled concentrations				
Ultrafine particle 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 100,000 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
Distance to major roadways (freeways, highways and major arterials)				
<50 m	70,003		1.044 (1.022; 1.068)	<0.01
<100 m	70,003		1.023 (1.004; 1.042)	0.02
<150 m	70,003		1.008 (0.990; 1.027)	0.37
<200 m	70,003		1.007 (0.988; 1.026)	0.47
<250 m	70,003		1.006 (0.985; 1.027)	0.58
<300 m	70,003		1.013 (0.989; 1.037)	0.29

[a] Odds ratios were estimated using generalized additive mixed models with random effects per hospital. 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.

[b] IQR: inter-quartile range increase in exposure; units are micrograms per cubic meter for all particulate mass and elements and part per billion for gaseous pollutants. Ultrafine particle number is expressed in number per cm^3.

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