Title

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Publication Date

2014-10-01

DOI
10.1016/j.envres.2014.05.003

Environmental Research ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008

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ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form
9 April 2014
Accepted 4 May 2014

Keywords:
Air pollution
Birth weight
Source
Speciation
Ultrafine particle

ABSTRACT

Background: Low birth weight (LBW, <2500 g) has been associated with exposure to air pollution, but it is still unclear which sources or components of air pollution might be in play. The association between ultrafine particles and LBW has never been studied.

Objectives: To study the relationships between LBW in term born infants and exposure to particles by size fraction, source and chemical composition, and complementary components of air pollution in Los Angeles County (California, USA) over the period 2001–2008.

Methods: Birth certificates ($n=960{,}945$) were geocoded to maternal residence. Primary particulate matter (PM) concentrations by source and composition were modeled. Measured fine PM, nitrogen dioxide and ozone concentrations were interpolated using empirical Bayesian kriging. Traffic indices were estimated. Associations between LBW and air pollution metrics were examined using generalized additive models, adjusting for maternal age, parity, race/ethnicity, education, neighborhood income, gestational age and infant sex.

Results: Increased LBW risks were associated with the mass of primary fine and ultrafine PM, with several major sources (especially gasoline, wood burning and commercial meat cooking) of primary PM, and chemical species in primary PM (elemental and organic carbon, potassium, iron, chromium, nickel, and titanium but not lead or arsenic). Increased LBW risks were also associated with total fine PM mass, nitrogen dioxide and local traffic indices (especially within 50 m from home), but not with ozone. Stronger associations were observed in infants born to women with low socioeconomic status, chronic hypertension, diabetes and a high body mass index.

Conclusions: This study supports previously reported associations between traffic-related pollutants and LBW and suggests other pollution sources and components, including ultrafine particles, as possible risk factors.

1. Introduction

Intrauterine growth restriction and resulting low birth weight (LBW, defined as birth weight less than 2500 g) have been associated with increased risks of chronic diseases in later life such as the metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases, (Chernausek, 2012), but also wheezing and asthma in childhood (Caudri et al., 2007). Air pollution induces oxidative stress, inflammation (Schlesinger et al., 2006) and hemodynamic changes, which are suspected to impair oxygen and nutrient transport to the fetus, and in turn, intrauterine growth (Kannan et al., 2006). Results from a growing number of epidemiological studies do suggest that exposure of pregnant women to air pollution may result in higher risks of LBW (Dadvand et al., 2013; Pedersen et al., 2013; Stieb et al., 2012).

Abbreviations: LBW, low birth weight; IQR, inter-quartile range; OR, odds ratios; CI, confidence intervals; $PM_{2.5}$, particulate matter of less than 2.5 μm in aerodynamic diameter; $PM_{0.1}$, particulate matter of less than 0.1 μm in aerodynamic diameter; EBK, empirical Bayesian kriging; UCD_P, University of California Davis/CIT_Primary chemical transport model; CTM, chemical transport models; NO_2, nitrogen dioxide; O_3, ozone; FRC, Functional Road Classes; BMI, body mass index; EC, elemental carbon; OC, organic carbon; LUR, land use regression; PAH, polycyclic aromatic hydrocarbons

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http://dx.doi.org/10.1016/j.envres.2014.05.003
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Please cite this article as: Laurent, O., et al., Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ. Res. (2014), http://dx.doi.org/10.1016/j.envres.2014.05.003

However, associations between air pollution exposure and LBW differ widely depending on study settings and designs (Brauer et al., 2008; Laurent et al., 2013).

It is suspected that the different definitions of air pollution metrics partly contribute to discrepancies in the literature (Dadvand et al., 2013). Characterizing exposure to air pollution is challenging and the different exposure assessment methods present advantages and limitations (e.g., in terms of temporal and spatial resolutions). Consequently, assessing the consistency of epidemiological results obtained using complementary exposure metrics can be useful to draw more informed conclusions. For instance, in Los Angeles positive associations were observed between the risk of preeclampsia and ambient nitrogen oxides concentrations, whether these concentrations were estimated by monitoring station measurements, land use regression or deterministic modeling, which strengthened confidence in this finding (Wu et al., 2011b).

Particulate matter (PM) has various core compositions and absorbs transition metals, polycyclic aromatic hydrocarbons (PAHs) and other organic compounds, that are able to generate oxidative stress and inflammation to various extents (Schlesinger et al., 2006; Delfino et al., 2010). Differences in PM composition have therefore been hypothesized to modify the relationship between total PM mass and LBW (Ebisu and Bell, 2012). Notable spatial contrasts in PM composition have been documented across the U.S. (Bell et al., 2007). However, few studies investigated the relation between PM composition and birth weight (Bell et al., 2010, 2012; Darrow et al., 2011; Ebisu and Bell, 2012), probably because of the scarcity of particle speciation data.

There are also open questions, of direct relevance to policy, on the sources of air pollution most likely to generate detrimental effects on pregnancy outcomes. Recent publications have suggested a possible influence of primary emissions from traffic on LBW (e.g.: Laurent et al., 2013; Wilhelm et al., 2012). Such an influence is biologically plausible since some components of primary traffic emission (e.g.: organic compounds such as PAHs, elemental carbon, trace metals) promote systemic inflammation and decrease antioxidant enzyme activity (Delfino et al., 2010). The possible influence of other sources of air pollution (e.g.: wood burning and meat cooking, that notably generate PAHs and other organic compounds) has also been suggested (Boy et al., 2002; Wilhelm et al., 2012). However, only one study attempted to assess simultaneously the relative contributions from different sources to the risk of LBW (Wilhelm et al., 2012), probably since results from source apportionment methods (e.g.: Chemical Mass Balance or Positive Matrix Factorization) are relatively rare and remain site-specific.

Chemical transport models (CTMs) have been used to address issues of the lack of source information and measurement scarcity for certain air pollutants (Hu et al., 2014a). For instance CTMs can predict the detailed size and chemical composition of primary PM with reasonable temporal and spatial resolution, while keeping track of source information. This approach can also apply to particles of certain size fractions for which direct measurement data are usually too rare to be directly usable in epidemiological studies, such as particles less than 0.1 μm in aerodynamic diameter ($PM_{0.1}$) (Abernethy et al., 2013). Concerns exist about the toxicity of $PM_{0.1}$ due to their specific properties (potential for translocation into the blood or other organs than lung, large number concentration and surface-to-volume ratio) (Knol et al., 2009). To the best of our knowledge, the relationship between birth weight and $PM_{0.1}$ has never been studied.

This work aimed at studying the relationships between air pollution and LBW in term born infants in Los Angeles County, California. It extends previous research on this topic, by using spatiotemporal chemical transport modeling of primary particles by source and composition and by studying $PM_{0.1}$ exposure. It also makes use of more commonly used air pollution metrics such as interpolated measurement data, traffic indices and proximity to roads. This allows for comparison of results according to complementary exposure metrics for traffic-related air pollution.

2. Methods

2.1. Study population

Birth certificate records for all births occurring from January 1, 2001 to December 31, 2008 to women residing in Los Angeles County (n=1,203,782) were obtained from the Health Information and Research Section at the California Department of Public Health. Multiple births (n=35,213) were excluded along with infants with recorded birth defects or unknown birth defects status (n=3353 and n=398, respectively). Births with missing information for gestational age (n=62,724), or implausible combinations of birth weight and gestational age (Alexander et al., 1996) were also excluded (n=4995). Further, infants born before 260 or after 308 estimated days of gestation (n=141,485 and n=22,839 respectively) were excluded (Bell et al., 2010). Several exclusion criteria overlapped for certain births, leaving 960,945 births for analyses.

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. In total, we had 53% of addresses geocoded to a specific parcel, 42.5% using address range interpolation,[1] 4.5% at the Zip code centroid level, and 0.05% at the city centroid.

2.2. Air pollution metrics

2.2.1. Chemical transport modeling

The University of California Davis/CIT_Primary (UCD_P) chemical transport model (Hu et al., 2014a) estimated primary ground-level PM element concentrations across densely populated areas of California including Los Angeles County at a 4 km × 4 km grid resolution for particles ranging from 0.01 to 20 μm from approximately 900 sources. In the present study, the simulated PM concentrations were calculated for two particle size fractions ($PM_{2.5}$ and $PM_{0.1}$) for the period of 2000–2006. The UCD_P model was developed to track primary PM (emitted directly from sources) through a simulation of emission, advection, diffusion and deposition. The detailed descriptions of the model and its validation are the purpose of other publications (Hu et al., 2014a, 2014b), but its main components are summarized below.

Size and composition resolved particle emissions were derived from a library of primary particle source profiles measured during actual source tests. Gridded emissions were prepared using the raw emissions inventory provided by the California Air Resources Board (Hu et al., 2014a). Meteorological inputs were prepared using the Weather Research and Forecast (WRF) model version 3.1 (Skamarock et al., 2008). Published papers describe the bulk advection and turbulent diffusion algorithm (Kleeman and Cass, 2001), the dry deposition approach (Kleeman et al., 1997), the vertical advection scheme (Hu et al., 2010), and the wet deposition scheme (Mahmud et al., 2010) used in the model. Every source with a unique emissions inventory code (EIC) in the emissions database was tracked separately through model simulations. In the present study, we defined seven broad source categories, namely gasoline, diesel, shipping, high sulfur combustion sources (including aircraft, electricity generation, petroleum refining and other industries), commercial meat cooking, wood burning, and other sources. The mass and density of size-resolved PM were tracked during model calculations, with composition profiles applied during post-processing of results. UCD_P only tracked primary PM and did not account for the formation of secondary PM produced by chemical reactions in the atmosphere, which might have different health effects (Delfino et al., 2010) and will be studied in future works.

Women living in each of the 448 model grid cells covering Los Angeles County (see Appendix Fig. A.1) at the time of delivery were assigned daily concentrations estimated for the corresponding cell, which were then averaged for specific pregnancy periods (entire pregnancy, 1st, 2nd or 3rd trimester).

2.2.2. Monitoring station measurements

Measurements from government monitoring stations for the period 2000–2008 were obtained from the California Air Resources Board for total $PM_{2.5}$, nitrogen

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[1] If no parcel match could be found for an address, an approximate location for this address was determined by using the address range for the matched street segment – the location was determined by computing where the address would fall as a proportion of the total address range associated with the appropriate side of the street segment. This proportion was then applied to the total length of the street segment (Goldberg et al., 2007).

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dioxide (NO_2) and ozone (O_3). Only results from filter-based measurements, generally conducted every 3 or 6 day, were included for $PM_{2.5}$. Hourly NO_2 and O_3 measurements were converted to daily means using a criterion of 75% daily data completeness at 24-h basis. Only data for the 10 AM–6 PM time windows were used to calculate daily means for O_3. Monthly averages for pollutants were then calculated for stations with more than 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 Spock, 2007) implemented in ArcGIS 10.1 (ESRI, Redlands, CA). EBK accounts for the uncertainty of semivariogram estimation by a process of subsetting and simulations. Due to a high computational cost, we conducted 100 variogram simulations for monthly averaged concentrations only. Pollutant surface predictions and their associated variance (reflecting the uncertainty in variogram estimation and subsequent predictions) were generated for 200 m × 200 m grids. The EBK was applied for the entire California, where the number of available monitors with valid measurements for each pollutant varied during the study period. The ranges of available monitors per month were 75–98 for $PM_{2.5}$, 151–182 for O_3 and 94–109 for NO_2. Our study region (Los Angeles County) had 5–11 monitors for $PM_{2.5}$, 12–16 for O_3, and 11–16 for NO_2 (see Appendix Fig. A.1). Final pollutant concentration estimates were calculated for each mother by weighing monthly average concentrations by the number of days of each month during pregnancy or specific pregnancy trimesters (Wu et al., 2011b).

2.2.3. *Traffic and roadways*

Traffic indicators are crude proxies for emission sources of traffic-related pollutants (Wilhelm and Ritz, 2003) but might capture - though imperfectly - small-scale variations in primary traffic emissions (e.g.: $PM_{0.1}$ EC, trace metals) which were modeled only at coarser resolutions in this study. Traffic densities within circular buffers of different sizes (radii from 50 m to 350 m with a 100 m increment) 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 based on 2002 AADT were then scaled to other years based on temporal trends in total vehicle miles traveled in Los Angeles County (CALTRANS, 2013).

TeleAtlas street data (ESRI, 2010) were used to calculate the distance from each maternal home to the nearest freeway or highway (defined by categories of Functional Road Classes(FRC) A0–A3), and the nearest major road (FRC A0–A5). The same road data were used to calculate the total length of major road segments within 50–350 m around homes.

2.3. *Statistical analyses*

Generalized additive models as implemented in the “mgcv” package (version 1.7-18) of the R environment (version 2.15.1) were used to study the relationships between air pollution metrics and term LBW. A logistic link function with a quasi-binomial distribution was used, given observed under-dispersion (scale parameter ≤ 0.2). In the main models, maternal race/ethnicity, educational level, parity, the trimester of pregnancy during which primary care began and infant's gender were adjusted for using categorical variables. Maternal age, length of gestation and median household income by Census Block Group (U.S. Census Bureau, 2004) were adjusted for using smoothing splines, given their J-shape relationships with LBW. For pollutant concentrations interpolated by EBK, regressions were weighted by the inverse variance of pollutant predictions. For temporally-varied exposure, we conducted analyses for entire pregnancy exposures, then for each pregnancy trimester. We explored the shapes of the relationships between air pollution metrics and LBW using smoothing splines, and generally observed no major departure from linearity (see Appendix Fig. A.2). We therefore introduced most air pollution metrics as linear terms in the models and then report related odds ratios (OR) for LBW per an inter-quartile range (IQR) in air pollution metrics, with 95% confidence intervals (CI). Distance to roadway was analyzed using dichotomous indicators for living or not living within certain distances (i.e. 50, 100, 150 m) from roads.

In sensitivity analyses, we examined the effects of further adjustment for population density, diabetes (pre-pregnancy and gestational combined), chronic hypertension and preeclampsia. We explored the influence of controlling for both seasonal and long-term temporal trends by adjusting for a smoothed function of the day of conception, with four degrees of freedom per year (Barnett et al., 2011). In the subset of infants born in 2007 and 2008, we examined the effects of adjustment for maternal height, body mass index (BMI) at the beginning of pregnancy and weight gain during pregnancy, which were only recorded on birth certificate during these two years. Further, we explored the influence of geocoding accuracy, by analyzing the subgroup of births geocoded at the exact parcel centroid.

We investigated potential effect modifications by maternal race/ethnicity, education, median block group income, hypertension, diabetes (pre-pregnancy and gestational combined) and preeclampsia. In the 2007–2008 births subsets, effect modification by maternal BMI at the beginning of pregnancy was explored, using categories defined by Abrams and Parker (1988) (see Table 1), with and without adjusting for maternal height and weight gain during pregnancy. As the inter-quartile range in exposure differs between subgroups defined by categories of potential effect modifiers, we present all results of subgroup analyses standardized to the IQR in exposure observed for the entire population.

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

3. Results

The mean birth weight among term born infants was 3390.1 g (standard deviation: 459.8 g) and 22,420 (2.33%) of them had a

Table 1
Study population of term born infants and their mothers.

Characteristics	Subjects	% Low birth weight (< 2500 g)
Infant's gender		
Female	472,743	2.68
Male	488,200	2.00
Unknown	2	–
Maternal education		
Lower than 8th grade	116,894	2.42
9th Grade to high school	454,558	2.55
College (< 4 years)	173,184	2.19
College (≥ 4 years)	202,944	1.89
Unknown	13,365	2.93
Maternal race/ethnicity		
African American	65,308	4.41
Asian	103,045	2.76
Hispanic	606,609	2.24
Caucasian	168,086	1.63
Multiple/other	14,478	2.21
Unknown	3419	1.96
Parity		
Primparous	378,639	2.89
Multiparous	581,845	1.97
Unknown	461	6.29
Trimester primary care began		
First	74,138	2.25
Second	78,425	2.91
Third	13,944	3.15
None	2,072	8.01
Unknown	7081	3.29
Maternal age		
< 20	92,125	3.19
20–44	867,093	2.24
≥ 45	1727	3.42
Median income by census block group		
\$2499–27,000	238,336	2.70
\$27,007–36,875	239,896	2.44
\$36,888–50,650	240,475	2.26
\$50,652–200,001	240,376	1.94
Unknown	1862	1.77
Diabetes		
Yes	22,086	2.38
No	938,849	2.33
Chronic hypertension		
Yes	2054	6.28
No	958,881	2.32
Preeclampsia		
Yes	12,605	9.00
No	948,339	2.24
Pre-pregnancy body mass index (2007–2008 data only)		
≤ 19.9	25,240	3.47
20–24.9	86,812	2.31
25–29.9	53,731	2.01
30–34.9	24,361	1.78
> 35	14,385	1.93
Unknown	38,402	2.37

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LBW. Maternal educational level was missing for 1.4% of the subjects (Table 1). The proportion of missing data was even lower for other variables, except for maternal height, weight at the beginning of pregnancy, and gestational weight gain (9.2%, 13.8%, and 15.3% respectively) in 2007–2008 data. The proportion 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. The proportion of LBW by maternal characteristics, diseases and median income level follows the expected directions (Table 1).

Appendix, Table A.1 presents the mean and correlation of each exposure metric used in the study. Total $PM_{2.5}$ and NO_2 interpolated by EBK were strongly positively correlated, and both were negatively correlated with O_3. Total $PM_{2.5}$ was moderately correlated with primary $PM_{2.5}$ modeled by UCD_P ($R=0.49$) and was weakly correlated with traffic density, road length and distance to roads ($R \leq 0.20$). UCD_P predictions of primary PM from several sources were highly correlated with each other – gasoline and diesel ($R=0.96$), meat cooking and gasoline or diesel ($R=0.86$), mass from all sources and from sources classified as "other" ($R=0.96$ and 0.89 for $PM_{2.5}$ and $PM_{0.1}$ respectively). Gasoline and diesel contributed respectively to 8% and 21% of the total $PM_{2.5}$ primary mass, and to 12.5% and 24% of the total $PM_{0.1}$ primary mass. Contributions from meat cooking, wood burning, high sulfur sources and shipping were respectively around 15%, 8%, 6% and 3% for each PM fraction.

The correlations between primary $PM_{2.5}$ and $PM_{0.1}$ for the same source were above 0.87. The correlations between $PM_{2.5}$ and $PM_{0.1}$ for a same chemical species (contributions from all sources being summed) ranged from 0.67 to 1. Traffic density and road length were only slightly correlated with pollutant concentrations interpolated by EBK or with predicted primary $PM_{2.5}$ and $PM_{0.1}$ from all sources ($|R| \leq 0.23$). Correlations between road length and traffic density within a same buffer size ranged from 0.53 (50 m buffer) to 0.62 (350 m buffer). Distance to roadways was negatively but moderately correlated with all other exposure metrics ($|R| \leq 0.32$), except O_3 ($R=0.20$).

For the entire pregnancy exposure, a 2.5% increase in risk of term LBW was associated with an inter-quartile range increase in primary $PM_{2.5}$ or $PM_{0.1}$, for all sources summed. Significant associations of similar magnitudes were also observed for primary PM from each specific source, except shipping (Table 2). Gasoline was the PM source most strongly associated with LBW, followed by wood burning and meat cooking. Among the chemical species studied, increased LBW risk was associated with elemental and organic carbon (EC, OC), potassium, iron, manganese and nickel in both particle fractions. Increased LBW risk was also associated with titanium and copper in $PM_{2.5}$ and chromium in $PM_{0.1}$. Associations with UCD_P predictions were overall stronger for third trimester exposures (Appendix, Table A.2).

For EBK-interpolated measurements, we observed a significant increase in LBW risk for total $PM_{2.5}$, but not O_3 or NO_2 (Table 2). The OR for total $PM_{2.5}$ was of similar magnitude to that observed for primary $PM_{2.5}$ or $PM_{0.1}$ estimated by the UCD_P model. Trimester-specific results revealed patterns similar to those for the entire pregnancy period (Appendix, Table A.2). However, for the third trimester exposure only, a significantly increased LBW risk was associated with NO_2, whereas a significantly decreased risk was associated with O_3.

Small yet statistically significant increases in LBW risk were associated with increases in traffic density and total road length within 50 m buffers. For road length, an increased LBW risk was also significant for a 150 m buffer. Living within 50 m and 100 m of any major road was associated with a 6% (95% CI: 4–7%) and 3% (95% CI: 2–4%) increase in LBW risk respectively. The increase was 7% (95% CI: 1–13%) for living within 50 m of a freeway or highway (Table 2).

Adjustment for population density, diabetes, chronic hypertension, preeclampsia, maternal height, pre-pregnancy BMI or weight gain during pregnancy changed ORs by 1% or less (data not shown). The influence of adjustment for time of conception was also weak, except that for wood burning it yielded increased odds ratios, from about 2% to 5–6% increase in risk per IQR in exposure (Appendix Table A.3). Restricting analyses to births geocoded to the exact parcel centroid reduced the study population by half, but did not substantially change the distribution of maternal age, education or race/ethnicity. In this subgroup with the best geocoding accuracy, ORs remained positive and significant for primary PM from gasoline, diesel, meat cooking and all sources grouped, road length within 50 and 150 m buffers and living with 50 m of major roadway or freeways. Contrarily to the main analysis, traffic density within 150–350 m buffers but not 50 m was associated with increased LBW risk (data not shown).

For analyses stratified by maternal race/ethnicity, most significant associations between LBW and primary PM were observed in infants of Hispanic mothers (Appendix Table A.4). Increased risks associated with NO_2 were observed in infants of Hispanic and African Americans mothers, whereas increased risks associated with O_3 were observed in infants of White non-Hispanic mothers. A few unexpected significant decreases in risk were observed notably in infants of Asian mothers for PM, O_3 and NO_2, and of White non-Hispanic mothers for traffic density and road length in 250 and 350 m buffers.

For analyses stratified by maternal education, significant and generally stronger associations with EBK-interpolated $PM_{2.5}$ and NO_2 and with primary particles were observed for the lowest educational levels subgroups (Appendix Table A.5). For traffic and road indices, overall more significant increases in risk were observed in subgroups with higher education. However, statistical power was lower in the group with the lowest educational level. Analyses stratified by quartile of block group median income did not reveal any marked pattern (data not shown).

Stronger associations between LBW and air pollution were observed in women with than without chronic hypertension, for most exposure metrics considered (see Appendix Table A.6). Stronger associations were also observed in women with than without diabetes for ozone, traffic and road indexes, but patterns were less clear for other exposure metrics (Appendix Table A.7). No consistent pattern was observed by preeclampsia status (Appendix Table A.8). In 2007–2008 data, the risk of LBW associated with EBK-interpolated $PM_{2.5}$ consistently increased from the lowest to the highest pre-pregnancy BMI category. This pattern persisted after further adjustment for maternal diseases, height and weight gain (data not shown). No such pattern was observed for O_3 or NO_2 (Appendix Table A.9).

4. Discussion

This is one of the first studies relating term LBW with concentrations of primary particle by source and composition and to the best of our knowledge, the first study of $PM_{0.1}$ and LBW. The results show modest increases in the risk of LBW associated with primary $PM_{2.5}$ and $PM_{0.1}$ from all sources except shipping and with several chemical species (EC, OC, potassium, iron, manganese, chromium, nickel, copper and titanium) in primary PM. Increased LBW risks are also associated with total $PM_{2.5}$ interpolated by EBK, with NO_2 in the last pregnancy trimester, and with local traffic indicators. Several population subgroups with potentially higher susceptibility were identified – infants of mothers with a lower education, Hispanic ethnicity, diabetes, chronic hypertension, and a high BMI.

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Table 2
Odds ratios for LBW associated with air pollution metrics (pregnancy-long exposure).

	Subjects	IQR[a] in exposure	OR[b] per IQR[a] (95% CI[c])	IQR[a]in exposure	OR[b] per IQR[a] (95% CI[c])
UCD_P primary particles predictions		**$PM_{2.5}$**		**$PM_{0.1}$**	
Sources					
High sulfur sources	704,148	0,4431	1.010 (1.005, 1.015)	0,0515	1.014 (1.008, 1.020)
Meat cooking	704,148	0,5219	1.019 (1.013, 1.025)	0,0588	1.019 (1.013, 1.025)
Gasoline	704,148	0,2908	1.028 (1.019, 1.037)	0,0560	1.028 (1.019, 1.037)
Wood burning	704,148	0,4606	1.020 (1.010, 1.031)	0,0875	1.026 (1.014, 1.037)
Diesel	704,148	0,6903	1.016 (1.009, 1.024)	0,1006	1.016 (1.009, 1.024)
Shipping	704,148	0,0976	1.001 (0.999, 1.003)	0,0129	1.001 (0.999, 1.003)
All	704,148	2,8762	1.025 (1.017, 1.033)	0,4271	1.027 (1.019, 1.034)
Species					
Elemental Carbon	704,148	0,4380	1.016 (1.008, 1.023)	0,0612	1.016 (1.008, 1.023)
Organic Carbon	704,148	1,2744	1.031 (1.023, 1.040)	0,2495	1.032 (1.023, 1.040)
Potassium	704,148	0,0215	1.016 (1.008, 1.025)	0,0018	1.026 (1.017, 1.035)
Chromium	704,148	0,0025	1.002 (0.997, 1.006)	0,0003	1.007 (1.001, 1.012)
Iron	704,148	0,0836	1.020 (1.011, 1.028)	0,0017	1.005 (1.000, 1.010)
Titanium	704,148	0,0030	1.003 (1.000, 1.006)	0,0001	1.002 (0.999, 1.004)
Arsenic	704,148	0,0012	1.002 (0.999, 1.006)	0,0001	1.002 (0.999, 1.006)
Manganese	704,148	0,0017	1.008 (1.003, 1.014)	0,0001	1.007 (1.002, 1.012)
Copper	704,148	0,0023	1.010 (1.004, 1.017)	0,0001	1.002 (0.997, 1.007)
Nickel	704,148	0,0021	1.009 (1.003, 1.015)	0,0003	1.009 (1.004, 1.014)
Lead	704,148	0,0048	1.001 (0.995, 1.008)	0,0004	1.001 (0.995, 1.008)
	Subjects	**IQR[a] in exposure**	**OR[b] per IQR[a] (95% CI[c])**		**OR[b] per IQR[a] (95% CI[c])**
Pollutants concentrations interpolated by empirical Bayesian Kriging					
$PM_{2.5}$	938,629	5.82	1.020 (1.010, 1.031)		
O_3	938,629	8.62	0.992 (0.984, 1.001)		
NO_2	938,629	7.36	1.008 (0.999, 1.017)		
Traffic density				**Distance to roads (dichotomized exposure)**	
Buffer size				Major roads	
50 m	938,629	5,657	1.005 (1.003, 1.008)	< 50m	1.056 (1.041, 1.071)
150m	938,629	20,073	1.001 (0.997, 1.006)	< 100m	1.033 (1.020, 1.046)
250m	938,629	16,642	0.997 (0.993, 1.001)	< 150m	1.007 (0.993, 1.020)
350m	938,629	14,303	0.999 (0.996, 1.003)		
Road length					
Buffer size				Highway/freeway	
50 m	938,629	28	1.016 (1.013, 1.020)	< 50m	1.074 (1.015;1.135)
150m	938,629	383	1.016 (1.007, 1.024)	< 100m	0.979 (0.949; 1.010)
250m	938,629	595	1.001 (0.995, 1.007)	< 150m	0.969 (0.946; 0.992)
350m	938,629	1,107	1.004 (0.998, 1.010)		

[a] IQR: inter-quartile range. Units are microgram per cubic meter for particles.

[b] OR: odds ratio estimated by generalized additive models adjusting for maternal race/ethnicity, education, parity, trimester primary care beginning, infant's gender, maternal age, length of gestation and median income by census Block Group

[c] CI: confidence interval

Long-term measurements for PM speciation or for $PM_{0.1}$ mass are very limited (Abernethy et al., 2013; Bell et al., 2007). Chemical transport modeling is an alternative approach to address the lack of measurement data and to link pollutant concentrations with specific sources. The resolution of 4 km × 4 km grid cells is coarse as compared with, for instance, spatial variations of ultrafine particle number emitted by traffic sources (Karner et al., 2010). Still, this approach allowed reflecting spatial contrasts at broader scales, that would not be captured by central site monitors (Hu et al., 2014a), and allowed including all births in Los Angeles County, whether mothers were living close to a monitor or not.

Detailed discussions on uncertainties in UCD_P predictions associated with model inputs and treatment on various processes have been presented in Hu et al. 2014a; Hu et al. 2014b. The UCD_P model includes all the important processes for primary PM, but does not include secondary aerosol formation, coagulation, and nucleation. Sensitivity analyses indicate that these omitted processes have important contribution to total PM (primary+secondary), but generally have a less than 10% impact on annual average primary PM concentrations (Hu et al., 2014b). The WRF predicted wind field, one of the key meteorological parameters for determining the primary PM concentrations, is generally biased high on stagnant days, leading to under-prediction of high primary pollution events. Uncertainties in emissions, such as lack of high temporal resolution of residential sources and incomplete chemical source profiles for 157 sources, also lower the model ability to reproduce some of the observed strong day-to-day variations. As a result, model predictions are in better agreement with measurements over longer averaging time (e.g., ≥ 1 month) than when day-to-day variations are considered. For instance, longer averaging time increased the overall correlation for $PM_{2.5}$ EC from 0.89 (1 day) to 0.94 (1 month), and overall increased the number of species with strong correlations (Hu et al., 2014b). The present study focused on exposure averaged on the entire pregnancy period and on specific pregnancy trimesters, which should minimize the impact of errors in the prediction of daily variations.

A complete validation study for the UCD_P predictions, including comparisons between predictions by source and the results of source apportionment studies conducted at five locations throughout California and during different episodes, has been conducted (Hu et al., 2014a). Excellent agreements were observed between source contributions modeled by UCD_P and estimated by chemical mass balance models, for mobile sources and wood burning.

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The degree of agreement was also good for meat cooking, except in a specific rural setting (Angiola). This however might be due to high uncertainties in the measurement of cholesterol, that was used as an organic marker for meat cooking (Hu et al., 2014a). The agreement between modeled concentrations and the results of source apportionment studies across several locations and in different episodes builds our confidence in the model results at other locations and time.

In the analyses, we decided a priori to include only PM components for which correlations between monthly averaged predictions and measured values (both in $PM_{2.5}$, since measurement results for most components were available only for that fraction) were >0.6 in Los Angeles. Correlations were >0.8 for EC, potassium, chromium, iron, arsenic, manganese, copper, nickel and lead in $PM_{2.5}$ (Hu et al., 2014b). No validation results were available for primary OC because secondary formation accounts for a significant fraction of total OC mass. $PM_{0.1}$ mass prediction agreed well with available measurements across all Californian sites (that were available from the literature and had varying temporal resolution, from 3 days to 5 months, $R=0.92$). EC was the only $PM_{0.1}$ component for which the correlation between UCD_P prediction and measurements could be evaluated, and this was also found to be high ($R=0.94$, $N=8$ sites) (Hu et al., 2014a). There is greater uncertainty in the metal composition results for $PM_{0.1}$ than for $PM_{2.5}$, since insufficient $PM_{0.1}$ metal measurements were available for validation with robust statistical analysis. This is likely due to the difficulty in measuring minute quantities of elemental species in the $PM_{0.1}$ size fraction (Hu et al., 2014a). Predictions for metals in $PM_{0.1}$ might be correct but could not be rigorously evaluated so far and were thus left unconstrained.

Presently, our findings based on primary particles by source and composition can only be compared to a few other studies that were all based on measured $PM_{2.5}$ data. Bell et al. (2010, 2012) studied the associations between term LBW and $PM_{2.5}$ by source and composition averaged at the county resolution from monitoring station measurements in four Connecticut and Massachusetts counties. This research was later extended to the Northeastern and Mid-Atlantic regions of the US for $PM_{2.5}$ composition (Ebisu and Bell, 2012). In Los Angeles County, Wilhelm et al. (2012) conducted a similar study but assigned exposure based on 22-months of monitoring station data for women living within 8 km of the stations. In Atlanta, Darrow et al. (2011) assigned $PM_{2.5}$ element concentrations measured at one central site to subjects living within five surrounding counties. The European ESCAPE and LISA studies examined PM absorbance, a marker for elemental carbon (Pedersen et al., 2013; Slama et al., 2007). Despite exposure metrics of different natures in these studies, their results are qualitatively consistent with ours for $PM_{2.5}$ EC (Bell et al., 2010; Darrow et al., 2011; Ebisu and Bell, 2012; Pedersen et al., 2013; Slama et al., 2007; Wilhelm et al., 2012), potassium (Bell et al., 2012), iron (Bell et al., 2010), titanium (Bell et al., 2012; Ebisu and Bell, 2012) and nickel (Bell et al., 2010; Ebisu and Bell, 2012). No studies that examined $PM_{2.5}$ OC reported significant associations (Darrow et al., 2011; Ebisu and Bell, 2012; Wilhelm et al., 2012). However, these studies relied on measured data with a large portion of secondary OC, whereas UCD_P modeled only primary OC. In Atlanta, the summed mass of several water soluble metals in $PM_{2.5}$ (chromium, copper, iron, manganese, nickel and vanadium) was associated with a decrease in mean birth weight (Darrow et al., 2011). The same exposure metric (excluding vanadium, which contributes very little to mass) was associated with an increase in LBW risk in our study (data not shown). Some studies suggest possible influences of chromium (Junaid et al., 1996) on birth weight reduction in animals. In summary, our analyses identified a number of chemical species as potentially harmful. However, observed associations might be misleading if these species are strongly correlated with other pollutants that increase LBW risk, for instance if they share common sources, similar dispersion patterns and chemical properties. Therefore, these results call for confirmation in other study settings.

Analyses of PM by source revealed positive associations between LBW and PM from most evaluated sources. These findings are supported by other studies for meat cooking and 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 wood burning (Boy et al., 2002). Fast food restaurants and road traffic are both important contributors to $PM_{0.1}$ emissions (Abernethy et al., 2013) and $PM_{0.1}$ might be the pollutant causing the association between these sources and LBW. However, primary $PM_{2.5}$ and $PM_{0.1}$ from meat cooking and from traffic are very strongly correlated (across sources and fractions), making it difficult to disentangle the influence of each source and each fraction. Most of particle emissions from meat cooking are due to commercial meat cooking in our study setting. Commercial meat cooking and traffic sources likely correlate in space, since commercial restaurants and fast-food stores may be more densely located in areas with a dense transportation network due to marketing reasons. Positive associations were also observed between LBW and $PM_{2.5}$ or $PM_{0.1}$ from high sulfur sources, which include a wide variety of sources (e.g., electricity generation, petroleum refining, aircraft). Conducting more thorough investigations by source subtype would be needed to get more insight into these observed associations.

The EBK approach we used to interpolate measured pollutants concentrations allowed retaining both their temporal and spatial variability. However, because of its high computational cost, temporal variability in air pollution measurement was not considered at a finer than monthly resolution. In order to estimate the impact of the resulting approximation in exposure calculation on odds ratio estimates, we compared results obtained using UCD_P daily estimates and monthly estimates. As expected, estimating exposure for the entire pregnancy period by using daily data (Table 2) yielded very similar results to those obtained when exposure data were previously averaged by calendar month (Appendix Table A.10). Differences in odds ratios were generally not visible after 3-digit rounding. Such differences were also slight when pregnancy trimesters were considered (Appendix Table A.11)

For the spatial resolution, EBK does not incorporate spatial covariates for prediction as would do land use regression or cokriging models. It therefore models the general trends in spatial variations. For this reason, we only applied EBK to pollutants that exhibit strong regional trends ($PM_{2.5}$, O_3 and NO_2). EBK-produced variance maps reflect the uncertainty in prediction estimates. However, weighting regressions by the inverse of this variance had no noticeable influence on ORs and only slightly reduced confidence intervals (data not shown). A previous study in Los Angeles County identified an association between LBW and total $PM_{2.5}$ during the third trimester only (Ghosh et al., 2012), whereas we observed significant associations for exposure during the entire pregnancy and each pregnancy trimester. This previous study however was restricted to subjects living within 8 km from monitoring stations (Ghosh et al., 2012). The EBK approach allowed including all Los Angeles County births, yielding greater statistical power.

The finer the spatial resolution of the exposure metrics considered (e.g., traffic density indices, road length and distance to roads), the more important the precision of subject geocoding. After restricting analyses to subjects with the best geocoding precision (exact parcel), associations remained significant for road length within a 50 m buffer and for living within 50 m of a major road (the OR even increased to 13% (95% CI: 4–22%) for “living within 50 m of a freeway or highway”). Traffic density was not

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associated with LBW risk anymore for a 50 m buffer. Loss of statistical power due to reduced sample size might have contributed to this change. Our findings of increased LBW risk for living within 50 m of highways or freeways are supported by similar findings from Vancouver, Canada (Brauer et al., 2008). Other studies failed to detect such associations (Barnett et al., 2011). However, the rarity of this exposure situation makes it less likely for smaller cohorts to detect a slight association with LBW. The observed associations in close proximity to traffic sources are of particular interest since a recent study identified truck route length within 50 m of measurement sites as a major determinant of $PM_{0.1}$ number concentrations (Abernethy et al., 2013).

Our study has some limitations. The personal exposure of mothers during pregnancy could not be estimated in this large cohort since we had no time-activity information and pollution levels can vary substantial among micro-environments (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.

While socio-demographic data in birth certificates are thought to be accurate, more uncertainty surrounds the completeness of maternal diseases reporting, and of gestational age estimates that were mostly based on reported last menstrual period. Adjusting for maternal height, pre-pregnancy BMI and weight gain did not markedly modify ORs. Data on maternal smoking during pregnancy were also available for years 2007 and 2008, but these data were not used because of potentially serious under-reporting by comparison with other sources (California Department of Health Services, 2006). The lack of adequate data to adjust for maternal smoking is probably the major limitation of this study. In California, the prevalence of smoking during pregnancy was lowest in Hispanic women ($<6\%$) (California Department of Health Services, 2006), the subgroup in which we observed the highest ORs and that represents more than 60% of the study population. We adjusted for major determinants of maternal smoking associated with air pollution exposure – age, race/ethnicity and socioeconomic status (Murin et al., 2011). We can however not exclude a possible influence of smoking on our results.

Higher ORs were observed in infants of mothers with chronic hypertension and with diabetes (for ozone and traffic indexes only for the latter). These original findings are potentially of high public health interest. However because of potential under-reporting, it is uncertain to which extent women with reported diseases on birth certificates are representative of all women suffering from these diseases. Higher ORs for total $PM_{2.5}$ in women with higher BMI also constitute an original finding. Both obesity and exposure to air pollution are associated with systemic inflammation (Kannan et al., 2006; Rodriguez-Hernandez et al., 2013), that is a hypothesized pathway to LBW (Kannan et al., 2006). Inflammation is also a common feature of hypertension and diabetes (Rodriguez-Hernandez et al., 2013). Further research would be necessary to confirm effect modification of the relationships between air pollution and LBW by hypertension, diabetes and BMI, and if confirmed, to investigate inflammation as a possible mechanism for such interactions.

5. Conclusions

This study is the first to report a positive association between exposure to $PM_{0.1}$ and term LBW. Several chemical species in PM were also identified as potentially harmful, in broad agreement with recent research. Consistent results obtained using complementary exposure matrices support previous evidence that primary traffic-related pollutants might increase LBW risk. The suggested influence of other sources such as commercial meat cooking and wood burning constitutes emerging evidence that deserves further investigation. Several population subgroups with potentially higher susceptibility were identified – infants of mothers with a lower education, Hispanic ethnicity, diabetes, chronic hypertension and high BMI.

Competing interests

The authors have no conflict of interest to disclose.

Approval by committee for human subjects research

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

Acknowledgments

The authors thank Beate Ritz (UCLA) and Ralf Delfino (UCI) for helping to start the study and Scott Bartell (UCI) for providing statistical advice. They also want to thank the Health Information and Research Section/California Department of Public Health for providing birth certificates data.

The study was supported by the Health Effects Institute (HEI 4787-RFA09-4110-3 WU).

The authors are responsible for the analyses, interpretations, and conclusions, which do not necessarily reflect the views of the Health Effects Institute or of the Health Information and Research Section/California Department of Public Health.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.05.003.

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