Environmental Research 142 (2015) 354–364

Contents lists available at ScienceDirect

Environmental Research

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

Modeling spatial effects of $PM_{2.5}$ on term low birth weight in Los Angeles County

Eric Coker [a,*], Jokay Ghosh [b], Michael Jerrett [c], Virgilio Gomez-Rubio [d], Bernardo Beckerman [c], Myles Cockburn [e], Silvia Liverani [f], Jason Su [c], Arthur Li [g], Molly L Kile [a], Beate Ritz [b,1], John Molitor [a,1]

[a] College of Public Health and Human Sciences, Oregon State University, Corvallis, OR, USA
[b] School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA
[c] School of Public Health, University of California, Berkeley, Berkeley, CA, USA
[d] Department of Mathematics, Universidad De Castilla-La Mancha, Albacete, Spain
[e] Preventive Medicine and Spatial Sciences, University of Southern California, Los Angeles, CA, USA
[f] Department of Mathematics, Brunel University, London, United Kingdom
[g] Department of Information Science, City of Hope National Cancer Center, Duarte, CA, USA

ARTICLE INFO

Article history:
Received 15 April 2015
Received in revised form
27 June 2015
Accepted 30 June 2015

Keywords:
Air pollution
$PM_{2.5}$
Term low birth weight
Spatial effects
Multilevel modeling

ABSTRACT

Air pollution epidemiological studies suggest that elevated exposure to fine particulate matter ($PM_{2.5}$) is associated with higher prevalence of term low birth weight (TLBW). Previous studies have generally assumed the exposure–response of $PM_{2.5}$ on TLBW to be the same throughout a large geographical area. Health effects related to $PM_{2.5}$ exposures, however, may not be uniformly distributed spatially, creating a need for studies that explicitly investigate the spatial distribution of the exposure–response relationship between individual-level exposure to $PM_{2.5}$ and TLBW. Here, we examine the overall and spatially varying exposure–response relationship between $PM_{2.5}$ and TLBW throughout urban Los Angeles (LA) County, California. We estimated $PM_{2.5}$ from a combination of land use regression (LUR), aerosol optical depth from remote sensing, and atmospheric modeling techniques. Exposures were assigned to LA County individual pregnancies identified from electronic birth certificates between the years 1995-2006 ($N=1{,}359{,}284$) provided by the California Department of Public Health. We used a single pollutant multivariate logistic regression model, with multilevel spatially structured and unstructured random effects set in a Bayesian framework to estimate global and spatially varying pollutant effects on TLBW at the census tract level. Overall, increased $PM_{2.5}$ level was associated with higher prevalence of TLBW county-wide. The spatial random effects model, however, demonstrated that the exposure–response for $PM_{2.5}$ and TLBW was not uniform across urban LA County. Rather, the magnitude and certainty of the exposure–response estimates for $PM_{2.5}$ on log odds of TLBW were greatest in the urban core of Central and Southern LA County census tracts. These results suggest that the effects may be spatially patterned, and that simply estimating global pollutant effects obscures disparities suggested by spatial patterns of effects. Studies that incorporate spatial multilevel modeling with random coefficients allow us to identify areas where air pollutant effects on adverse birth outcomes may be most severe and policies to further reduce air pollution might be most effective.

1. Introduction

Extensive evidence indicates that prenatal exposure to outdoor air pollution is associated with risk of term low birth weight (Brauer et al., 2008; Fleischer et al., 2014; Ghosh et al., 2013, 2012; Hyder et al., 2014; Padula et al., 2012; Parker et al., 2011; Ponce, 2005; Proietti et al., 2013; Ritz and Wilhelm, 2008; Shah and Balkhair, 2011; Stieb et al., 2012; Wilhelm et al., 2011; Wu et al., 2011). While TLBW contributes to racial–ethnic and socioeconomic health disparities in the United States, air pollution is thought to be an important place-based factor in the complex geography of and susceptibly to TLBW (Jerrett and Finkelstein, 2005; Morello-Frosch and Shenassa, 2006). It is reasonable to consider, however, that air pollution exposure–response effects on adverse birth outcomes, such as TLBW, vary spatially within an urban setting.

* Corresponding author.
E-mail address: cokerer@onid.orst.edu (E. Coker).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.envres.2015.06.044

First and foremost, air pollutant mixtures or components of PM air pollution can be autocorrelated spatially within urban environments – depending on local-scale air pollution sources, the intensity of emissions, and meteorology (among other factors) (Hajat et al., 2013; Molitor et al., 2011; Su et al., 2012). As a result, the intrinsic toxicity of $PM_{2.5}$ mixtures is likely to be spatially dependent. For instance, Laurent et al. (2014) found that various components and sources of fine PM air pollution, which exhibit strong spatially varying characteristics, produced statistically significant gradients in PM-related TLBW risk in LA County. Similarly, Wilhelm et al., (2011), found that the exposure–response between $PM_{2.5}$ and TLBW varied by $PM_{2.5}$ source type (e.g. gasoline versus geologic sources) within LA County. Furthermore, Pedersen et al. (2015) studied eight European birth cohorts and found that the exposure–response between $PM_{2.5}$ was dependent on its chemical composition, with OR estimates for sulfur $PM_{2.5}$ of 1.24, compared to 1.08 for overall $PM_{2.5}$. Such local-scale intra-urban differences in particulate air pollution exposure and health effects patterns may therefore lead to inequalities with regard to PM-related adverse birth outcome risks (Baxter et al., 2007). Further, a wide range of contextual neighborhood factors and individual factors that are spatially correlated, from socioeconomic status (SES), demographics (i.e. racial segregation), exposure to violence (Messer et al., 2006), access to healthy food (Lane et al., 2008) or green space (Hystad et al., 2014), housing characteristic, and psychosocial, may contribute to variations in susceptibilities to air pollution that are not fully accounted for in standard regression models relying on fixed covariate effects (Morello-Frosch and Shenassa, 2006). Few studies, however, have been conducted to examine whether there is a spatial patterning – or a "risk-scape" (Morello-Frosch and Shenassa, 2006) – for PM-related birth outcomes. While previous health research has evaluated the spatial dependency of PM-related chronic health effects such as cardiovascular disease and asthma (Boehm Vock et al., 2014; Choi et al., 2009; Fuentes et al., 2006; Jerrett et al., 2005; Krewski et al., 2009; McConnell et al., 2010; Samoli et al., 2004; Shankardass et al., 2009), no studies have modeled the spatial dependency of individual-level $PM_{2.5}$ exposure–response relationships on birth outcomes.

Several recent studies examined the spatial variation in $PM_{2.5}$ effects on TLBW between different countries or between US states. A large collaborative multi-site international study found a substantial degree of heterogeneity in estimates for entire pregnancy exposure–response between study sites, despite the use of similar exposure assessments and statistical models in the studies (Dadvand et al., 2013; Parker et al., 2011). Hao et al. (2015) found substantial differences between states in the U.S. in terms of the magnitude and direction of effects of $PM_{2.5}$ on TLBW. Another multi-state U.S. study also found that the size of exposure–response estimates for $PM_{2.5}$ and TLBW depended upon study site; with odds ratios ranging from between 0.942 (95% CI: 0.817, 1.09) in Utah to as high as 1.72 (95% CI: 1.55, 1.93) in New York state (per 10-unit increase in $PM_{2.5}$ exposure) (Harris et al., 2014). Additionally, Williams et al. (2007) demonstrated, through implementation of a multilevel linear random coefficient model, that adverse effects on average birth weight in a population varied by census tract due to hazardous air pollution emitting industrial sites. The observed statistically significant differences in effect size between census tracts remained significant even after adjusting for the number of hazardous sites per census tract, individual level confounders, and contextually relevant census tract level confounding factors (Williams et al., 2007).

Despite the recent evidence suggesting that air pollution-related adverse effects on birth weight may vary spatially, no studies have explicitly examined spatial variation in effects within a dense metropolitan region such as LA county, which we are targeting in our paper. Our guiding hypothesis is that modeling of the spatially varying coefficients will show differences in TLBW according to LA County census tracts and thus provide evidence for localized $PM_{2.5}$ exposure–response. Specifically, the magnitude of effect will be higher in some census tracts when compared to the global mean exposure–response for all of urban LA County. Our approach goes beyond the commonly employed estimation of an overall average $PM_{2.5}$ effect on birth weight and will allow us to describe a spatially-patterned deviation from the average effects, thus pinpointing potential 'hotspots' within LA County where the magnitude and probability of $PM_{2.5}$ effects are likely to be strongest.

In our paper we utilize an existing land use regression (LUR) $PM_{2.5}$ exposure model within a multi-level Bayesian framework; implemented with spatially-dependent random coefficients. This information may be useful from a policy perspective to create targeted public health interventions for LA County.

2. Methods

2.1. Study population and birth outcomes

Data on infant birth weight were derived from electronic birth certificates provided by the California Department of Public Health, for LA County births between 1/1/1995 and 12/31/2006 ($N=1{,}522{,}084$). The birth records provided information on maternal characteristics such as age, race/ethnicity, education, total number of previous maternal births, and residential address, as well as characteristics of the infant (abnormalities, birth season, gestational age at birth, birth weight and baby sex). Human subjects research was approved through the University of California, Los Angeles' Office of the Human Subjects Protection Program, the California Committee for the Protection of Human Subjects, and the University of Southern California Office for the Protection of Research Subjects. Similar to previous studies, we restricted the dataset to singleton births with no recorded abnormalities (Ghosh et al., 2013, 2012; Wilhelm et al., 2011). Additionally, we excluded births with extreme gestational days (less than 140 days or greater than 320 days), births that were not full term (<259 gestation days), and births with birth weight less than 500 g or greater than 5000 g due to concerns about recording errors. For our final analyses, we further excluded births without complete information on the full set of study covariates ($n=19{,}017$). Finally, since we are interested in estimating within-city spatial variation in $PM_{2.5}$ effects, the spatial analysis further excluded rural sub-region of LA County, thus leaving a final study population of $N=1{,}356{,}304$. A detailed description of methods for geocoding residential addresses are described elsewhere (Goldberg et al., 2008).

2.2. $PM_{2.5}$ exposure assessment

A $PM_{2.5}$ LUR model developed previously by (Jerrett et al., 2013) was used to estimate individual exposures to $PM_{2.5}$ at each mother residential address. Such estimates are intended to best represent spatially resolved long-term exposure to annual levels of $PM_{2.5}$ between 1995-2006, rather than pregnancy period-specific exposure. This $PM_{2.5}$ LUR model has been used previously to examine chronic long-term exposure to $PM_{2.5}$ and related health effects over time, in a large cohort study of California adults (Jerrett et al., 2013). This LUR method has been described in previous publications and the reader is referred to Beckerman et al. (2013) and Jerrett et al. (2013) for greater detail. Briefly, the predicted concentrations of $PM_{2.5}$ were based on covariate data from the following sources: (1) daily observations of $PM_{2.5}$ air monitoring collected between 1998–2002 at government monitoring sites throughout California, which was supplemented with remotely-sensed $PM_{2.5}$ data covering the time period between 2001 and

2006 (Beckerman et al., 2013); (2) data on traffic and road networks from 1990 to 2001; (3) land use data from the year 2001; (4) population density data from the 2000 US Census; and (5) numerical output from remote sensing modeling coupled with atmospheric modeling (Van Donkelaar et al., 2010). A deletion/substitution/addition algorithm was then implemented to develop the final model covariates with a cross-validated R^2 value of 0.65.

2.3. Covariates

Since this study is a methodological extension of previous work for the LA County area (Ghosh et al., 2012; Wilhelm et al., 2011), we applied similar covariates as in the previous studies to evaluate $PM_{2.5}$ in relation to risk of TLBW. Individual-level covariates were maternal age at delivery (<20 years, 20–24 years, 25–29 years, 30–34 years, ≥ 35 years), maternal race (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, and Other race), maternal years of education (<9 years, 9–12 years, 13–15 years, and ≥ 16 years), parity, gestational days, gestation days-squared (Ghosh et al., 2012; Wilhelm et al., 2011) and sex of the infant.

2.4. Statistical analysis

2.4.1. Standard analysis

While our main objective was to evaluate the spatial dependency of $PM_{2.5}$ effects on TLBW, we initially examined "global" (or L.A. County-wide) associations between $PM_{2.5}$ and TLBW using crude-unadjusted and multivariate adjusted logistic regressions techniques. The intent of implementing a global fixed effects model is to replicate exposure–response relationships between increasing $PM_{2.5}$ exposure and increasing prevalence of TLBW as demonstrated from previous research. The crude and multivariate models were implemented as a generalized linear model (*glm*) using the binomial family with the logistic function in the R statistical computing environment (R-version 3.1.2) (see Supplemental Materials for code describing the specific models employed in R (Everitt and Hothorn, 2010)). For consistency, the multivariate model utilized same fixed effects covariates as for the multilevel model described below.

2.4.2. Multilevel spatial modeling

The focus of the present study was to expand on previous work by implementing a multilevel spatial logistic regression model that would assess whether exposure–response relationships vary within L.A. County. Along with the fixed effects on the covariates, we simultaneously included a random effect coefficient for the census tract-level effect of $PM_{2.5}$ on log-odds of TLBW. The random air pollution effect coefficient is composed of a global intercept plus independent and spatial residual error terms via the Besag–York–Molly (BYM) model (Besag et al., 1991). Because this model includes both spatial and independently structured error terms, the data determined the extent of spatial smoothing employed, without requiring strong assumptions regarding residual spatial dependency. Further, this approach yields both a countywide global mean effect as well as census tract-level random coefficients indicating sub-regional (or census tract) effects of $PM_{2.5}$ on TLBW.

The variance structure of the spatial component of the BYM model requires specification of a spatial zero-one weight matrix of dimension J by J, where J is the number of census tracts. Each element i, j of the weight matrix is one if census tract i and j are adjacent to each other, and zero otherwise. The '*spdep*' package (*spdep* package version 0.5-77 obtained September 30 2014) in R (Bivand et al., 2013; Bivand and Piras, 2015) was used to construct this neighborhood weight matrix and we assigned neighbors based on queens adjacency, which is defined as any neighboring census tract with a shared edge or vertex for a given area (i.e. census tract).

In fitting the model, we took advantage of the computational efficiency of Integrated Nested Laplace Approximations (INLA, version 0.0-1420281647) estimation techniques as implemented in the well-established R-INLA package (Rue et al., 2015), which has been used in several recent studies of large dimensions (Bennett et al., 2014; Castelló et al., 2013; Lee et al., 2013; Lee and Mitchell, 2014). The INLA approach avoids the computational burden related to typical Markov Chain Monte Carlo techniques (Gilks et al., 1998) often used to fit Bayesian spatial models and allows accurate approximations to posterior marginal distributions of the model parameters (Grilli et al., 2014).

In the implementation of our model using R-INLA, the sub-regional-level air pollution effects consist of an overall fixed effect (that represents the overall mean effect) plus spatial and independent random residual effects as defined in the BYM model. (Rue et al., 2014, 2009; Martino and Rue, 2009). Hence, each Sub-Regional air pollution effect is then obtained as the sum of the overall fixed effect plus spatial and non-spatial census tract-level residual terms via the linear combination feature in R-INLA. This allows us to obtain a posterior distribution for each Sub-Regional-level air pollution effect, β_j, and to examine the spatial distribution of these effects throughout L.A. County.

The full model specification is presented in Eqs. (1) and (2) below. Our first-level logistic-regression model is,

$$\text{logit}(y_i) = V\boldsymbol{\eta}' + \beta_{z_i} x_i \tag{1}$$

where y_i denotes the logit probability of TLBW for individual i, $V\boldsymbol{\eta}'$ represents individual-level covariates V and associated fixed effect coefficients $\boldsymbol{\eta}'$, β_{z_i} represents sub-regional random effects of exposure, and x_i denotes individual-level $PM_{2.5}$ exposure. Note that $z_i = j$ indicates the census tract j to which individual i belongs, so if, say, individual 3 is in census tract number 12, then $z_3 = 12$, and $\beta_{z_3} = \beta_{12}$. There are therefore β_j, $j = 1, \ldots, J$ effects of $PM_{2.5}$ on log-odds of TLBW corresponding to each census tract, j.

We model the effects of $PM_{2.5}$ on TLBW for each census tract, j, as

$$\beta_j = \gamma_0 + S_j + \epsilon_j^{\beta} \tag{2}$$

where γ_0 is the overall region-wide $PM_{2.5}$ effect, and S_j and ϵ_j^{β} denote spatial and independent residual error terms, respectively, with the restriction $\sum_j S_j = 0$ imposed for indefinability reasons. While the independent error term is defined in the standard way as $\epsilon_j^{\beta} \sim N(0, \sigma_{\beta}^2)$, the spatial error term is defined as,

$S_{j|k\neq j} \sim N\left(\frac{\sum_{k\neq j} w_{jk} S_k}{\sum_{k\neq j} w_{jk}}, \frac{\tau^2}{\sum_{k\neq j} w_{jk}}\right)$, where the weights $w_{j,k}$ are elements of the zero-one neighborhood adjacency matrix defined to be equal to one when census tracts i, k are adjacent and zero otherwise. This approach has been successfully employed in a variety of exposure/health association studies. (see, for example, Molitor et al. (2007).)

2.5. Mapping

Estimates of the posterior quantities correspond to the adjusted random air pollution effects from the multilevel model were imported into ArcGIS 10.1 (ESRI, Redlands, CA) and merged with census tract boundary shapefiles to create exposure–response census tract-level 'effect maps'. In addition to mapping the multilevel adjusted census tract mean effects, the R-INLA package includes the 'inla.pmarginal' function that computes probabilities from the posterior distribution of the marginal random effects as obtained from the linear combinations described above. This enabled us to map the marginal probabilities that a given census tract random effect coefficient lies above zero, $P(\beta_j > 0)$. Similarly,

we mapped the probability that a given census tract random effect coefficient is above the adjusted global mean effect, $P(\beta_j > \bar{\beta})$. Computation of these probabilities help illustrate where associations between $PM_{2.5}$ and TLBW are most likely to occur (see Supplemental Materials for requisite R-INLA code needed to obtain posterior probabilities). Thus, our 'effect maps' depict probabilities that the $PM_{2.5}$ census tract-specific exposure–response (β_j) lies above zero (or an OR above 1) and the probability that a census tract-specific air pollution effect deviates from the overall average ($P(\beta_j > \bar{\beta})$).

3. Results

3.1. Descriptive analyses

Between 1995-2006 the overall prevalence of TLBW was 2.1% and the average $PM_{2.5}$ exposure was 17.04 μg/m^3 (interquartile range=16.25, 18.21). The spatial distribution of $PM_{2.5}$ concentrations indicated that exposures were highest within the urban core of LA County, specifically the southern, eastern, and northwest portions of urban LA (Supplemental Materials, Fig. S1). Risk factors that were associated with TLBW included maternal age, race, level of education, parity, gestation length (days), gestation squared, sex of the infant (Table 1), and were adjusted for in the following models.

3.2. $PM_{2.5}$ regression analyses

3.2.1. Standard logistic model

The final statistical analyses included 1,356,304 births from 2,033 LA County census tracts. In unadjusted fixed effects logistic regression, the odds of TLBW was 23.2% higher (OR=1.23 [95%CI: 1.16, 1.30]) per 10 μg/m^3 increase of $PM_{2.5}$. After adjusting for maternal age, race-ethnicity, education, parity, and infant gestation and sex, a 10 μg/m^3 increase in $PM_{2.5}$ exposure remained associated with statistically significant increased odds of TLBW (OR=1.17; 95%CI=1.10–1.24)(Table 2). The fully adjusted model results along with the model covariates are provided in detail within the Supplementary Material (Table S1, Supplementary Material).

Table 2
Association between $PM_{2.5}$ exposure and TLBW using standard and multilevel spatial regression methods (N=1,356,304).

Exposure	Standard model[a] OR (95% CI)[b]	Spatial multilevel model[a] OR (95% CI)[c]
$PM_{2.5}$ (per 10 μg/m^3)	1.17 (1.10, 1.24)[d]	1.19 (1.02, 1.39)

[a] Adjusted for sex of the infant, gestation age of infant, gestation age squared, maternal age, maternal race, maternal education level, and parity.
[b] OR per interquartile range=1.03 (95% CI: 1.02, 1.04), IQR=1.96 μg/m3.
[c] OR per interquartile range=1.05 (95% CI: 1.03, 1.08), IQR=1.96 μg/m3.
[d] For all of LA County, including rural areas, OR=1.17 (1.10–1.24).

3.2.2. Multilevel spatial model

The multilevel spatial model provides $PM_{2.5}$ coefficients on TLBW at a global county-wide level (Table 2) and at the census tract neighborhood level. The overall mean $PM_{2.5}$ exposure–response estimate for our multilevel spatial model was similar in magnitude to the fixed effect logistic regression result ($OR_{spatial}$=1.19 versus OR_{fixed}=1.17). The two maps presented in Fig. 1 and Fig. 3 present the probability that a given census tract air pollution effect (with outcome on log-odds scale) is above zero (Fig. 1) and the probability that a given census tract effect is above the estimated overall mean effect (Fig. 3), while Fig. 2 presents the mean $PM_{2.5}$ random effect per census tract.

For the probability effect map in Fig. 1, the census tracts in dark brown have a >95% probability of an effect that is above zero ($P(\beta_j > 0)$.). Thus, these areas represent census tracts where the $PM_{2.5}$ exposure–response with TLBW is most likely to be positive. The dark brown neighborhoods in Fig. 3 have a >95% probability for an effect above the county-wide (or "global") mean effect. Hence, these areas represent census tracts that are most likely to exhibit a $PM_{2.5}$ exposure–response that is greater in magnitude compared to the estimated mean exposure–response relationship, which we are considering to be 'hotspots' within the context of our study. The hotspots appear to be concentrated in census tracts within central and south-central LA County (Fig. 3).

Table 1
Demographic characteristics overall and by TLBW and crude odds ratios for TLBW (N=1,359,284).

Parameter	Overall (N=1,359,284)		TLBW Cases (N=27,714)		Non cases (N=1,331,570)		Crude TLBW
	n	% or mean (95% CI)	n	% (95% CI)	n	% (95% CI)	OR (95% CI)
Gestational age (days)		Mean=278.91 (278.92, 278.89)					
Sex of infant							
Male	688,568	50.66 (50.57, 50.74)	11,890	42.90 (42.32, 43.49)	676,678	50.82 (50.73, 50.90)	1.00
Female	670,716	49.34 (49.26, 49.43)	15,824	57.10 (56.51, 57.68)	654,892	49.18 (49.10, 49.27)	1.38 (1.34, 1.41)
Maternal age							
<20 years	143,265	10.54 (10.49, 10.59)	4090	14.76 (14.34, 15.18)	139,175	10.45 (10.40, 10.50)	1.00
20–24 years	318,122	23.40 (23.33, 23.47)	6959	25.11 (24.60, 25.62)	311,163	23.37 (23.30, 23.44)	0.76 (0.73, 0.79)
25–29 years	364,301	26.80 (26.73, 26.86)	6581	23.75 (23.25, 24.25)	357,720	26.86 (26.79, 26.94)	0.63 (0.60, 0.65)
30–34 years	322,341	23.71 (23.64, 23.79)	5674	20.47 (20.00, 20.95)	316,667	23.78 (23.71, 23.85)	0.61 (0.59, 0.64)
≥35 years	211,255	15.54 (15.48, 15.60)	4410	15.91 (15.48, 16.35)	206,845	15.55 (15.47, 15.60)	0.73 (0.69, 0.76)
Race–Ethnicity							
White	249,759	18.37 (18.31, 18.44)	3605	13.01 (12.61, 13.41)	246,154	18.49 (18.42, 18.55)	1.00
Hispanic	852,886	62.75 (62.66, 662.83)	16,260	58.67 (58.09, 59.25)	836,626	62.83 (62.75, 62.91)	1.33 (1.28, 1.38)
Black	107,237	7.89 (7.84, 7.93)	4175	15.06 (14.65, 15.49)	103,062	7.74 (7.69, 7.79)	2.77 (2.64, 2.89)
Asian	94,764	6.97 (6.93, 7.01)	2097	7.57 (7.26, 7.88)	92,667	6.96 (6.92, 7.00)	1.55 (1.46, 1.63)
Other	54,638	4.02 (3.99, 4.05)	1577	5.69 (5.42, 5.97)	53,061	3.98 (3.95, 4.02)	2.03 (1.91, 2.15)
Maternal education							
0–8 years	206,487	15.19 (15.13, 15.25)	4194	15.13 (14.71, 15.56)	202,293	15.19 (15.13, 15.25)	1.00
9–12 years	666,565	49.04 (48.95, 49.12)	14,867	53.64 (53.06, 54.23)	651,698	48.94 (48.86, 49.03)	1.10 (1.06, 1.14)
13–15 years	232,319	17.09 (17.03, 17.15)	4453	16.07 (15.64, 16.51)	227,866	17.11 (17.05, 17.18)	0.94 (0.90, 0.98)
≥16 years	253,913	18.68 (18.61, 18.75)	4200	15.15 (14.73, 15.58)	249,713	18.75 (18.69, 18.82)	0.81 (0.78, 0.85)
Parity							
0	522,598	38.45 (38.36, 38.53)	13,257	47.84 (47.25, 48.43)	509,341	38.25 (38.17, 38.33)	1.00
≥1	836,686	61.55 (61.47, 61.64)	14,457	52.16 (51.57, 52.75)	822,229	61.75 (61.67, 61.83)	0.68 (0.66, 0.69)

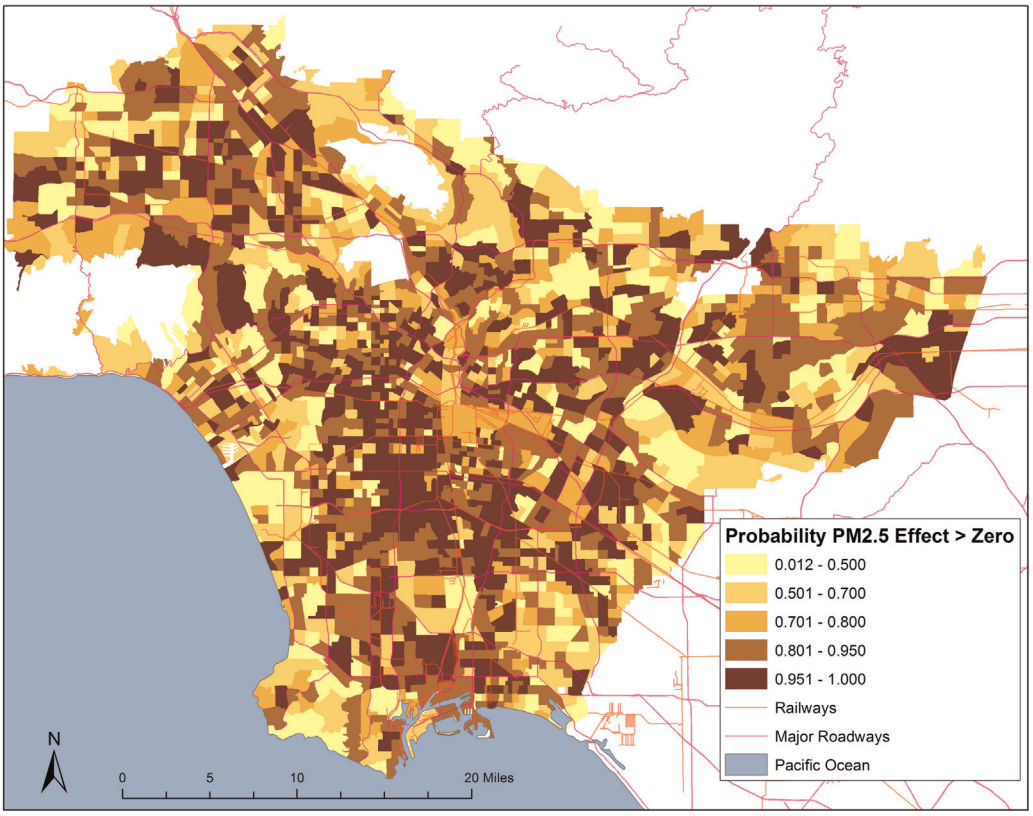

Fig. 1. Probability map for census tract $PM_{2.5}$ effects for TLBW ($P(\beta_j > 0)$) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation+gestation squared, and infant sex.

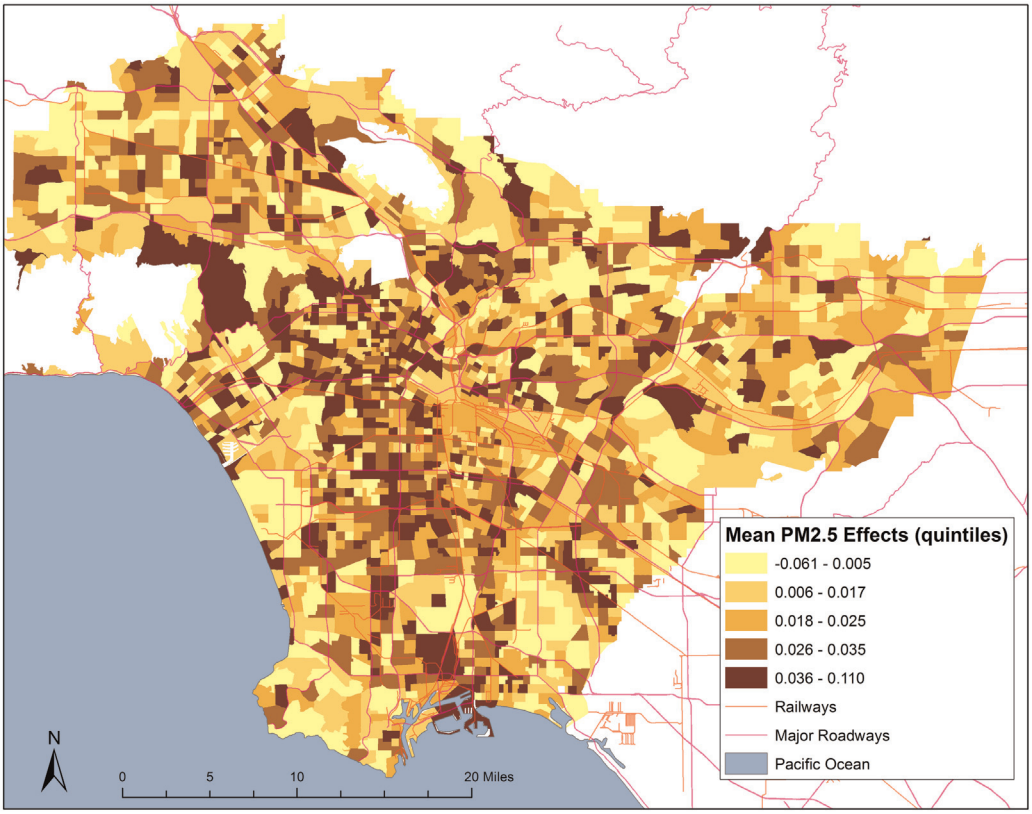

Fig. 2. Census tract $PM_{2.5}$ effects for TLBW (mean) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation+gestation squared, and infant sex.

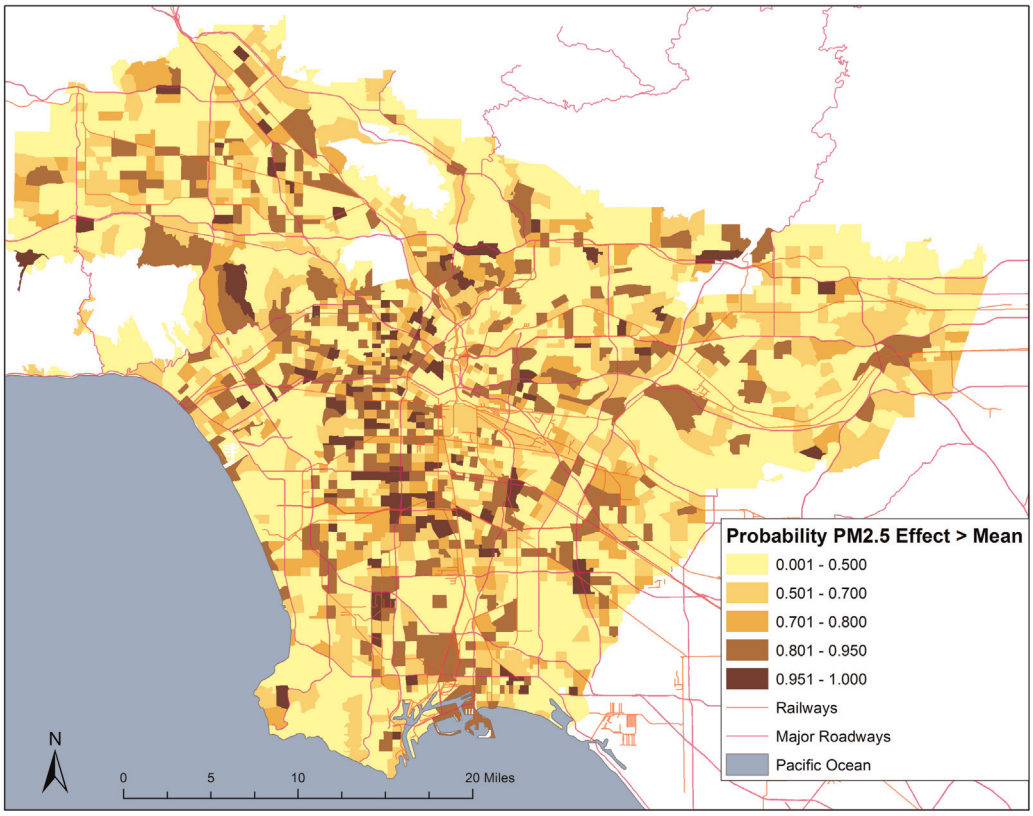

Fig. 3. Probability map for census tract $PM_{2.5}$ effects for TLBW ($P(\beta_j > \bar{\beta})$) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation + gestation squared, and infant sex.

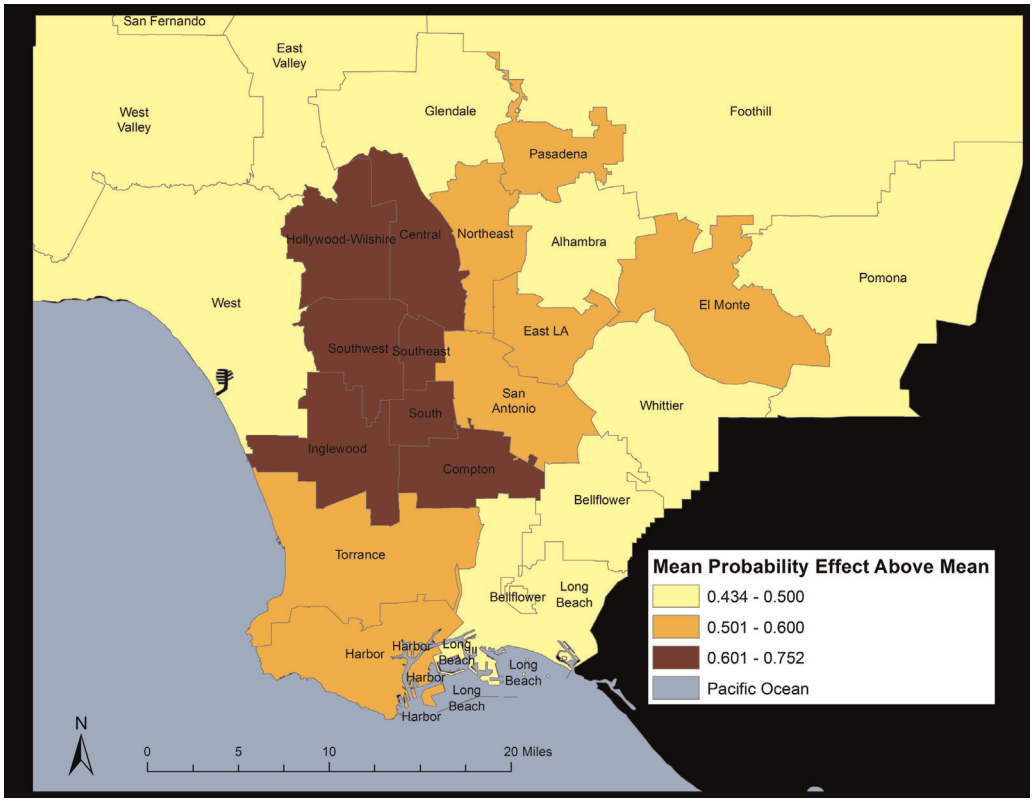

Fig. 4. Mean probabilities for census tract random effect above mean by LA County health districts.

3.2.3. LA health district summaries

LA County is composed of 26 health districts created from aggregates of census tract boundaries for the purposes of health assessments. Therefore, to highlight the observed spatial patterns in Fig. 3, from the posterior distribution of the marginal random effects we calculated and mapped the average probabilities for LA County health districts with respect to tract-level probabilities above the overall mean $PM_{2.5}$ coefficient. These numerical summaries are simply descriptive since they were acquired by calculating the mean tract-level probabilities. Health districts of LA urban core, including Central, Compton, Hollywood-Wilshire, Inglewood, South, Southeast, and Southwest health districts, are characterized by the highest probablities that the air pollution effect coefficients are above the overall mean coefficient (Fig. 4). Thus the map suggests effect 'hotspots' are concentrated within these health districts, which are generally lower income and non-white in terms of race-ethnicity (see Supplemental Materials, Figs. S2 and S3).

4. Discussion

4.1. Key findings

We applied Bayesian multilevel spatial modeling to examine whether the exposure–response relationship between $PM_{2.5}$ and TLBW varies spatially. Consistent with previous findings from LA County (Ghosh et al., 2012; Ritz et al., 2007; Wilhelm et al., 2011), we observed an overall relationship between increasing $PM_{2.5}$ exposure and increasing risk of TLBW. More important, we observed substantive variations across census tracts within LA County in the exposure–response between $PM_{2.5}$ and TLBW. Higher probabilities for positive $PM_{2.5}$ effects were mostly concentrated in central LA and south central LA sub-regions. Relative to the mean regional $PM_{2.5}$ effect on the log odds of TLBW, several census tracts located in central LA and south-central LA exhibited higher exposure–response relationships in terms of effect size and posterior probabilities for effects above the mean ($P(\beta_j > \bar{\beta})) > 0.95$). These observations suggested that $PM_{2.5}$ related adverse effects on birth weight may be modified by place.

A number of plausible explanations may account for the spatial patterning in the exposure–response between $PM_{2.5}$ exposures and TLBW observed in our study. Firstly, regionally varying and spatially correlated neighborhood contextual factors may enhance exposure gradients within an urban setting and other spatially structured individual factors may further create susceptibility to adverse birth outcome by interacting with $PM_{2.5}$. Regionally varying and overlapping aspects of neighborhoods with the potential to enhance exposure to air pollutants or susceptibility to air pollution related health effects may include (but are not limited to): built environment factors (i.e. age of homes, homes set back further from the curb along heavily trafficked roadways) (Ponce, 2005; Ramachandran et al., 2003); spatially correlated variation in the types of $PM_{2.5}$ sources (e.g. large truck traffic) and thus $PM_{2.5}$ component mixtures (Laurent et al., 2014; Wilhelm et al., 2011); the presence of older and higher pollution emitting vehicles, and neighborhood SES (Ponce, 2005). For example, Singer and Harley (2000) observed that older vehicles tended to emit higher air pollutant levels relative to newer vehicles within the LA area, and that vehicular emissions tended to be higher in low income areas compared to higher income areas (even for vehicles of the same age). Individual-level differences that display spatial clustering may also partially explain spatial patterns in birth outcomes risks; such as psychosocial (Ghosh et al., 2010), occupational (Horner and Mefford, 2007; Ritz et al., 2007), or nutritional factors (Jedrychowski et al., 2010; Lane et al., 2008), as well as individual home environments (i.e. home insulation or access to air conditioning (Ghosh et al., 2013; Jerrett et al., 2005; Ponce, 2005)). For instance, Ritz et al. (2007) found that parous women in LA without an occupation outside the home during the last 6 weeks of the pregnancy who were highly exposed to traffic-related air pollution had higher odds for preterm birth than exposed parous women working outside the home, illustrating the potential impact of exposure misclassification when using a home address. In another study we conducted in LA (Ponce, 2005) individuals' access to health insurance and their race, as well as neighborhood level factors such as SES and the physical environment (i.e. proximity to air pollution-related traffic and winter season) acted in concert to increase susceptibility to adverse pregnancy outcomes across LA county census tracts. Taken together this suggests a rather complex set of individual- and neighborhood-level social, cultural and environmental contributors to adverse birth outcomes that vary over space and may act on different biologic pathways to impair growth of the fetus resulting in TLBW, as suggested by the spatially varying effects estimated in our study.

In addition to spatial clustering of neighborhood and individual determinants and effect measure modifiers for birth outcomes, multi-pollutant mixtures in urban areas may create gradients in effects between Sub-Regions (Levy et al., 2013; Novák et al., 2014). While multi-pollutant mixtures may be more toxic in terms of birth outcomes, our study did not explicitly account for pollutant mixtures. While inclusion of a spatial random effects term may have mitigated this limitation to some extent – since multiple pollutant profiles have been observed to be clustered spatially (Austin et al., 2012) – this is an important limitation of this study. Furthermore, it cannot be ruled out that neighborhood-level and individual-level susceptibility and pollutant mixtures co-occur and together contribute to the observed spatially varying effect estimates seen in our study. Within regions of CA, such geographic-based susceptibility may be particularly acute. For instance, countywide studies in three California counties (Alameda, LA and San Diego) found that, while concentrations of individual pollutants such as diesel PM, NO_2, and $PM_{2.5}$ were statistically significantly higher within socio-economically disadvantaged compared to less disadvantaged communities, when cumulative exposures to diesel PM, NO_2, and $PM_{2.5}$ were considered, the relationship between SES and exposure was stronger (Su et al., 2012). Overlap of environmental and SES risk factors that can enhance neighborhood-level susceptibility has been reported previously (Jerrett and Finkelstein, 2005; Morello-Frosch and Shenassa, 2006).

4.2. Spatial dependency, air pollution, and birth outcome studies

A multilevel spatial hierarchical modeling approach is established as a flexible means of addressing spatial structure in the exposure–response relationship between air pollution and health effects (Boehm Vock et al., 2014; Dominici et al., 2000; Lee et al., 2013) and may therefore highlight notable localized effects (Chakraborty, 2012; Dominici et al., 2000; Earnest et al., 2007). A major statistical advantage gained in using this approach to modeling a spatially-structured exposure–response relationship is to maximize statistical power by using data in all sub-regions to inform the analysis, rather than calculating separate regression models for each sub-region (Gelman and Hill, 2006). Multilevel modeling approaches which incorporate spatial smoothing allow information from nearby regions to potentially exert more weight and influence compared to distant regions (Banerjee et al., 2004; Zhuoqiong, 2000).

A strength of our approach is the inclusion of individual-level pollutant effect estimates that are modeled with spatial structure at the census-tract level. Some air pollution and birth outcome studies have accounted for spatial dependency in the residuals, but still

assume a global effect due to exposure (Berrocal et al., 2011; Castelló et al., 2013; Thompson et al., 2014; Williams et al., 2007). A spatial correlated autoregressive (CAR) model has been applied by (Berrocal et al., 2011) to examine the effect of CT-level $PM_{2.5}$ on continuous birth weight in North Carolina. An important distinction between the present study and Berrocal et al (2011) is that we applied a spatially structured random air pollution effect term, whereas Berrocal et al (2011) implemented a random intercept and did not explore the possibility of geographic disparities in the PM exposure–response relationship. A study by Thompson et al. (2014) examined the exceedance probability of very LBW risks in relation to proximity to National Priorities List Superfund Sites in Texas by modeling the spatially structured error term using Poisson regression. This study, however, used aggregated outcomes for a given geographic area and did not include individual-level air pollution estimates of exposure. A study conducted in Spain that examined municipal-level risks of PTB and LBW with proximity to different types of industries modeled spatially varying effects using Poisson regression with a spatial error term and an unstructured error term (Castelló et al., 2013). A major difference in the Castelló et al. (2013) study is that these researchers, again, used aggregated outcome data and did not relate birth outcomes with individual-level estimates of air pollutant exposures. A study by Williams et al. (2007) applied a linear hierarchical random effects model with spatially unstructured random coefficients and found substantial variation across census tracts regarding the estimated effects of maternal residential proximity to hazardous air pollution sites for reducing average birth weight. Our results also found varying effects by census tract; however, Williams et al (2007) did not use air pollution estimates but rather the proxy measure of spatial proximity to hazardous air pollution emitting sites and did not apply spatial structure to the random coefficients. While it is clear from these studies that multilevel modeling is capable of revealing important spatial processes regarding air pollution-related reductions in birth weight; our work goes beyond previous findings by not only applying spatial structure to pollutant effects but illustrating spatially varying effects while adjusting for individual level confounders.

4.3. Study limitations

Our study is limited by the presence of unmeasured confounders. Most notably we lack information on maternal smoking or maternal exposure to indoor smoking. However, our previous research (Ritz et al., 2007) found that adjustment for maternal or household smoking did not alter the strength of air pollution effects on adverse birth outcomes in LA County. Our study also did not account for spatially varying housing characteristics (e.g. age of housing stock, substandard housing, or lack of air conditioning) that could potentially exacerbate gradients in intra-urban exposures; even between neighborhoods with similar ambient PM concentrations (Baxter et al., 2007; Burgos et al., 2013; Clougherty et al., 2011; Jerrett and Finkelstein, 2005; Lv and Zhu, 2013; Meng et al., 2005; Ramachandran et al., 2003; Reid et al., 2009). Additionally, PM-related birth outcome risks may be modified by individual-level or neighborhood-level susceptibility factors that are often spatially patterned, such as SES, racial–ethnic status, maternal body mass index, maternal nutrition status, and other adverse neighborhood conditions, e.g., poor access to healthy foods or green spaces (English et al., 2003; Hystad et al., 2014; Jedrychowski et al., 2010; Kannan et al., 2006; Lakshmanan et al., 2015; Lane et al., 2008; Laurent et al., 2014; Ponce, 2005; Schempf et al., 2009).

While the $PM_{2.5}$ LUR estimates in our study best represents the spatial contrasts of chronic exposures at maternal residences throughout LA county, our estimates lacked the temporal resolution to consider exposures during specific pregnancy time periods. This limitation may obscure important biologic differences with regard to birth outcome risks associated with different trimester exposure windows. Studies that have relied upon nearest site monitors for $PM_{2.5}$ estimation (Ghosh et al., 2012; Wilhelm et al., 2011) are better equipped to capture the temporal contrasts in maternal exposures, however, these studies lacked the spatial resolution to assess spatially varying effects of $PM_{2.5}$. For instance, while $PM_{2.5}$ may be fairly homogenous over a large region, it is likely that local-scale sources of $PM_{2.5}$ pollution carry greater importance when examining spatially varying TLBW effects (Laurent et al., 2014, 2013). Therefore, it was determined that the value in obtaining high spatial resolution was an acceptable temporal tradeoff, given the nature of our research question. Furthermore, we are confident in the ability of our exposure model to assess TLBW risks since our overall fixed effect $PM_{2.5}$ exposure–response estimate was consistent in terms of effect size when compared with previous research findings (Dadvand et al., 2013; Ghosh et al., 2012; Hyder et al., 2014; Laurent et al., 2014; Stieb et al., 2012; Wilhelm et al., 2011). For example, in the present study, we found an OR of 1.03 per *IQR* increase in maternal $PM_{2.5}$ exposure (Table 2). Ghosh et al. (2012) estimated maternal $PM_{2.5}$ concentrations, using an inverse distance weighting procedure based on governmental air monitoring stations for the years 2000-2006 in LA County, and found an OR of 1.04 per *interquartile range* (IQR) increase for entire pregnancy $PM_{2.5}$ exposure. Recently, Laurent et al. (2014) estimated an OR of 1.025 per IQR increase in maternal $PM_{2.5}$ exposure for LA County births between 2001 and 2008. Notably, Laurent et al. (2014) found that gasoline $PM_{2.5}$ exposure imparted the highest risk of TLBW compared to all other sources of $PM_{2.5}$ within LA. In a separate $PM_{2.5}$ and birth outcomes study, (Dadvand et al., 2013) pooled multiple $PM_{2.5}$ and TLBW analyses from seven different country study sites, despite large heterogeneity between the country-specific $PM_{2.5}$ effect estimates, they estimated a 10% (95%CI: 3%, 18%) adjusted increased odds of TLBW for a *10-unit* increase in $PM_{2.5}$ exposure, which is comparable to our finding of a 17% increase per *10-unit* increase in $PM_{2.5}$ exposure (Table 2).

4.4. Public health implications

Findings from our research is highly relevant to environmental health disparities and regulatory policy. First of all, our study implies that uniform regulatory standards geared towards reducing public health impacts from air pollution may not be sufficiently protective of susceptible sub-populations, and that such policies may need to be spatially tailored to protect these sub-populations. Secondly, our approach could identify 'hotspots' to help guide spatially targeted public health interventions intended to protect susceptible sub-populations from outdoor air pollution health effects (e.g., for example, by installing HEPA filters and air conditioning to reduce indoor exposures). Lastly, while our study found large within-county differences in effect estimates and thus the potential for $PM_{2.5}$ effect 'hotspots', additional data on potential modifying factors by neighborhood (i.e. $PM_{2.5}$ composition or neighborhood food environment) are needed to more fully explain the causes for this apparent spatial variation in the exposure–response relationship between $PM_{2.5}$ and TLBW.

5. Conclusion

We found that maternal exposure to $PM_{2.5}$ was associated with higher odds of TLBW in LA County. Moreover, our results indicate that the spatial patterning of the exposure–response relationship for $PM_{2.5}$ and TLBW needed to be considered. While previous research conducted in LA County has found variation of pollutant effects on adverse birth outcomes based on neighborhood factors

such as SES, our results take these previous findings a step further by identifying neighborhood TLBW 'hotspots' most likely to be affected negatively by air pollution. Also, compared to global effect estimates, our findings suggest the potential value of modeling spatial random air pollution effect coefficients in identifying disproportionately impacted communities as well the relative probability of localized exposure–response estimates. Finally, additional research is needed in hotspot areas to explore which spatially-based factors may help to better understand these differences between neighborhoods.

Acknowledgments

Research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.06.044.

References

Austin, E., Coull, B., Thomas, D., Koutrakis, P., 2012. A framework for identifying distinct multipollutant profiles in air pollution data. Environ. Int. 45, 112–121. http://dx.doi.org/10.1016/j.envint.2012.04.003.

Banerjee, S., Carlin, B.P., Gelfand, A.E., 2004. Hierarchical Modeling and Analysis for Spatial Data. Chapman & Hall/CRC, Boco Raton, Florida.

Baxter, L.K., Clougherty, J.E., Laden, F., Levy, J.I., 2007. Predictors of concentrations of nitrogen dioxide, fine particulate matter, and particle constituents inside of lower socioeconomic status urban homes. J. Expo. Sci. Environ. Epidemiol. 17, 433–444. http://dx.doi.org/10.1038/sj.jes.7500532.

Beckerman, B.S., Jerrett, M., Martin, R.V., van Donkelaar, A., Ross, Z., Burnett, R.T., 2013. Application of the deletion/substitution/addition algorithm to selecting land use regression models for interpolating air pollution measurements in California. Atmos. Environ. 77, 172–177. http://dx.doi.org/10.1016/j.atmosenv.2013.04.024.

Bennett, A., Yukich, J., Miller, J.M., Vounatsou, P., Hamainza, B., Ingwe, M.M., Moonga, H.B., Kamuliwo, M., Keating, J., Smith, T.A., Steketee, R.W., Eisele, T.P., 2014. A methodological framework for the improved use of routine health system data to evaluate national malaria control programs: evidence from Zambia. Popul. Health Metr. 12, 1–11. http://dx.doi.org/10.1186/s12963-014-0030-0.

Berrocal, V.J., Gelfand, A.E., Holland, D.M., Burke, J., Miranda, M.L., 2011. On the use of a $PM_{2.5}$ exposure simulator to explain birthweight. Environmetrics 22, 553–571. http://dx.doi.org/10.1002/env.1086.

Besag, J., York, J.C., Molli'e, A., 1991. Bayesian image restoration, with two applications in spatial statistics (with discussion). Ann. Inst. Stat. Math. 43, 1–59.

Bivand, R., Hauke, J., Kossowski, T., 2013. Computing the Jacobian in Gaussian spatial autoregressive models: an illustrated comparison of available methods: computing the Jacobian in spatial autoregressive models. Geogr. Anal. 45, 150–179. http://dx.doi.org/10.1111/gean.12008.

Bivand, R., Piras, G., 2015. Comparing implementations of estimation methods for spatial econometrics. J. Stat. Softw. 63, 1–36.

Boehm Vock, L.F., Reich, B.J., Fuentes, M., Dominici, F., 2014. Spatial variable selection methods for investigating acute health effects of fine particulate matter components. Biometrics 71, 167–177. http://dx.doi.org/10.1111/biom.12254.

Brauer, M., Lencar, C., Tamburic, L., Koehoorn, M., Demers, P., Karr, C., 2008. A Cohort study of traffic-related air pollution impacts on birth outcomes. Environ. Health Perspect. 116, 680–686. http://dx.doi.org/10.1289/ehp.10952.

Burgos, S., Ruiz, P., Koifman, R., 2013. Changes to indoor air quality as a result of relocating families from slums to public housing. Atmos. Environ. 70, 179–185. http://dx.doi.org/10.1016/j.atmosenv.2012.12.044.

Castelló, A., Río, I., García-Pérez, J., Fernández-Navarro, P., Waller, L.A., Clennon, J.A., Bolúmar, F., López-Abente, G., 2013. Adverse birth outcomes in the vicinity of industrial installations in Spain 2004–2008. Environ. Sci. Pollut. Res. 20, 4933–4946. http://dx.doi.org/10.1007/s11356-012-1444-5.

Chakraborty, J., 2012. Cancer risk from exposure to hazardous air pollutants: spatial and social inequities in Tampa Bay, Florida. Int. J. Environ. Health Res. 22, 165–183. http://dx.doi.org/10.1080/09603123.2011.628643.

Choi, J., Fuentes, M., Reich, B.J., 2009. Spatial–temporal association between fine particulate matter and daily mortality. Comput. Stat. Data Anal. 53, 2989–3000. http://dx.doi.org/10.1016/j.csda.2008.05.018.

Clougherty, J.E., Houseman, E.A., Levy, J.I., 2011. Source apportionment of indoor residential fine particulate matter using land use regression and constrained factor analysis: Indoor-source apportionment using LUR and factor analysis. Indoor Air 21, 53–66. http://dx.doi.org/10.1111/j.1600-0668.2010.00682.x.

Dadvand, P., Parker, J., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L.A., Gehring, U., Glinianaia, S.V., Gouveia, N., Ha, E., Leem, J.H., van den Hooven, E.H., Jalaludin, B., Jesdale, B.M., Lepeule, J., Morello-Frosch, R., Morgan, G.G., Pesatori, A.C., Pierik, F.H., Pless-Mulloli, T., Rich, D.Q., Sathyanarayana, S., Seo, J., Slama, R., Strickland, M., Tamburic, L., Wartenberg, D., Nieuwenhuijsen, M.J., Woodruff, T. J., 2013. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ. Health Perspect. 121, 267–373. http://dx.doi.org/10.1289/ehp.1205575.

Dominici, F., Samet, J.M., Zeger, S., 2000. Combinine evidence on air pollution and daily mortality from the 20 largest us cities: a hierarchical modelling strategy. J. R. Stat. Soc.: Ser. A (Stat. Soc.) 163, 263–302.

Earnest, A., Morgan, G., Mengersen, K., Ryan, L., Summerhayes, R., Beard, J., 2007. Evaluating the effect of neighbourhood weight matrices on smoothing properties of conditional autoregressive (CAR) models. Int. J. Health Geogr. 6, 54. http://dx.doi.org/10.1186/1476-072X-6-54.

English, P.B., Kharrazi, M., Davies, S., Scalf, R., Waller, L., Neutra, R., 2003. Changes in the spatial pattern of low birth weight in a southern California county: the role of individual and neighborhood level factors. Soc. Sci. Med. 56, 2073–2088. http://dx.doi.org/10.1016/S0277-9536(02)00202-2.

Everitt, B., Hothorn, T., 2010. A Handbook of Statistical Analyses Using R, 2nd ed. CRC Press, Boca Raton.

Fleischer, N.L., Merialdi, M., van Donkelaar, A., Vadillo-Ortega, F., Martin, R.V., Betran, A.P., Souza, J.P., O'Neill, M.S., 2014. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. Environ. Health Perspect. 122, 425–430 110. 1289/ehp.1306837.

Fuentes, M., Song, H.-R., Ghosh, S.K., Holland, D.M., Davis, J.M., 2006. Spatial association between speciated fine particles and mortality. Biometrics 62, 855–863. http://dx.doi.org/10.1111/j.1541-0420.2006.00526.x.

Gelman, A., Hill, J., 2006. Data Analysis Using Regression and Multilevel/Hierarchical Models, 1st edition. Cambridge University Press, Cambridge; New York.

Ghosh, J.K.C., Wilhelm, M.H., Dunkel-Schetter, C., Lombardi, C.A., Ritz, B.R., 2010. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles County mothers. Arch. Women's Ment. Health 13, 327–338. http://dx.doi.org/10.1007/s00737-009-0135-9.

Ghosh, J.K.C., Wilhelm, M., Ritz, B., 2013. Effects of residential indoor air quality and household ventilation on preterm birth and term low birth weight in Los Angeles County, California. Am. J. Public Health 103, 686–694. http://dx.doi.org/10.2105/AJPH.2012.300987.

Ghosh, J.K.C., Wilhelm, M., Su, J., Goldberg, D., Cockburn, M., Jerrett, M., Ritz, B., 2012. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. Am. J. Epidemiol. 175, 1262–1274. http://dx.doi.org/10.1093/aje/kwr469.

Gilks, W.R., Richardson, S., Spiegelhalter, D.J., 1998. Markov Chain Monte Carlo in Practice. Chapman & Hall/CRC, Boca Raton, FL.

Goldberg, D.W., Wilson, J.P., Knoblock, C.A., Ritz, B., Cockburn, M.G., 2008. An effective and efficient approach for manually improving geocoded data. Int. J. Health Geogr. 7, 60. http://dx.doi.org/10.1186/1476-072X-7-60.

Grilli, L., Metelli, S., Rampichini, C., 2014. Bayesian estimation with integrated nested Laplace approximation for binary logit mixed models. J. Stat. Comput. Simul., 1–9. http://dx.doi.org/10.1080/00949655.2014.935377.

Hajat, A., Diez-Roux, A.V., Adar, S.D., Auchincloss, A.H., Lovasi, G.S., O'Neilles, M.S., Sheppard, L., Kaufman, J.D., 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the multi-ethnic study of atherosclerosis (MESA). Environ. Health Perspect. 121, 1325–1333. http://dx.doi.org/10.1289/ehp.1206337.

Hao, Y., Strosnider, H., Balluz, L., Qualters, J.R., 2015. Geographic variation in the association between ambient fine particulate matter ($PM_{2.5}$) and term low birth weight in the United States. Environ. Health Perspect. [**Advanced Publication**], 1–28. http://dx.doi.org/10.1289/ehp.1408798.

Harris, G., Thompson, W.D., Fitzgerald, E., Wartenberg, D., 2014. The association of PM(2.5) with full term low birth weight at different spatial scales. Environ. Res. 134, 427–434. http://dx.doi.org/10.1016/j.envres.2014.05.034.

Horner, M.W., Mefford, J.N., 2007. Investigating urban spatial mismatch using job – housing indicators to model home – work separation. Environ. Plan. A 39, 1420–1440. http://dx.doi.org/10.1068/a37443.

Hyder, A., Lee, H.J., Ebisu, K., Koutrakis, P., Belanger, K., Bell, M.L., 2014. $PM_{2.5}$ exposure and birth outcomes: use of satellite- and monitor-based data. Epidemiology 25, 58–67. http://dx.doi.org/10.1097/EDE.0000000000000027.

Hystad, P., Davies, H.W., Frank, L., Van Loon, J., Gehring, U., Tamburic, L., Brauer, M., 2014. Residential greenness and birth outcomes: evaluating the influence of spatially correlated built-environment factors. Environ. Health Perspect. 122, 1095–1102. http://dx.doi.org/10.1289/ehp.1308049.

Jedrychowski, W., Perera, F., Mrozek-Budzyn, D., Flak, E., Mroz, E., Sochacka-Tatara, E., Jacek, R., Kaim, I., Skolicki, Z., Spengler, J.D., 2010. Higher fish consumption in

pregnancy may confer protection against the harmful effect of prenatal exposure to fine particulate matter. Ann. Nutr. Metab. 56, 119–126. http://dx.doi.org/10.1159/000275918.
Jerrett, M., Burnett, R.T., Beckerman, B.S., Turner, M.C., Krewski, D., Thurston, G., Martin, R.V., van Donkelaar, A., Hughes, E., Shi, Y., Gapstur, S.M., Thun, M.J., Pope, C.A., 2013. Spatial analysis of air pollution and mortality in California. Am. J. Respir. Crit. Care Med. 188, 593–599. http://dx.doi.org/10.1164/rccm.201303-0609OC.
Jerrett, M., Burnett, R.T., Ma, R., Pope, C.A., Krewski, D., Newbold, K.B., Thurston, G., Shi, Y., Finkelstein, N., Calle, E.E., Thun, M.J., 2005. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16, 727–736. http://dx.doi.org/10.1097/01.ede.0000181630.15826.7d.
Jerrett, M., Finkelstein, M., 2005. Geographies of risk in studies linking chronic air pollution exposure to health outcomes. J. Toxicol. Environ. Health A 68, 1207–1242. http://dx.doi.org/10.1080/15287390590936085.
Kannan, S., Misra, D.P., Dvonch, J.T., Krishnakumar, A., 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ. Health Perspect. 114, 1636–1642.
Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., Turner, M.C., Pope, C. A., Thurston, G., Calle, E.E., Thun, M.J., Beckerman, B., DeLuca, P., Finkelstein, N., Ito, K., Moore, D.K., Newbold, K.B., Ramsay, T., Ross, Z., Shin, H., Tempalski, B., 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res. Rep. Health Eff. Inst. 140, 5–114, discussion 115–136.
Lakshmanan, A., Chiu, Y.-H.M., Coull, B.A., Just, A.C., Maxwell, S.L., Schwartz, J., Gryparis, A., Kloog, I., Wright, R.J., Wright, R.O., 2015. Associations between prenatal traffic-related air pollution exposure and birth weight: modification by sex and maternal pre-pregnancy body mass index. Environ. Res. 137, 268–277. http://dx.doi.org/10.1016/j.envres.2014.10.035.
Lane, S.D., Keefe, R.H., Rubinstein, R., Levandowski, B.A., Webster, N., Cibula, D.A., Boahene, A.K., Dele-Michael, O., Carter, D., Jones, T., Wojtowycz, M., Brill, J., 2008. Structural violence, urban retail food markets, and low birth weight. Health Place 14, 415–423. http://dx.doi.org/10.1016/j.healthplace.2007.08.008.
Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J., 2014. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ. Res. 134, 488–495. http://dx.doi.org/10.1016/j.envres.2014.05.003.
Laurent, O., Wu, J., Li, L., Chung, J., Bartell, S., 2013. Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ. Health 12, 18. http://dx.doi.org/10.1186/1476-069X-12-18.
Lee, D., Mitchell, R., 2014. Controlling for localised spatio-temporal autocorrelation in long-term air pollution and health studies. Stat. Methods Med. Res. . http://dx.doi.org/10.1177/0962280214527384
Lee, D., Rushworth, A., Sahu, S., 2013. A Bayesian localised conditional auto-regressive model for estimating the health effects of air pollution. University of Glasgow, University of Southhampton.
Levy, I., Mihele, C., Lu, G., Narayan, J., Brook, J.R., 2013. Evaluating Multipollutant Exposure and Urban Air Quality: Pollutant Interrelationships. Neighborhood Variability, and Nitrogen Dioxide as a Proxy Pollutant. Environ. Health Perspect . http://dx.doi.org/10.1289/ehp.1306518.
Lv, J., Zhu, L., 2013. Effect of central ventilation and air conditioner system on the concentration and health risk from airborne polycyclic aromatic hydrocarbons. J. Environ. Sci. China 25, 531–536.
Martino, S., Rue, H., 2009. Implementing Approximate Bayesian Inference using Integrated Nested Laplace Approximation: a manual for the inla program.
McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., Gauderman, J., Avol, E., Künzli, N., Yao, L., Peters, J., Berhane, K., 2010. Childhood incident asthma and traffic-related air pollution at home and school. Environ. Health Perspect. 118, 1021–1026. http://dx.doi.org/10.1289/ehp.0901232.
Meng, Q.Y., Turpin, B.J., Korn, L., Weisel, C.P., Morandi, M., Colome, S., Zhang, J.J., Stock, T., Spektor, D., Winer, A., Zhang, L., Lee, J.H., Giovanetti, R., Cui, W., Kwon, J., Alimokhtari, S., Shendell, D., Jones, J., Farrar, C., Maberti, S., 2005. Influence of ambient (outdoor) sources on residential indoor and personal $PM_{2.5}$ concentrations: analyses of RIOPA data. J. Expo. Anal. Environ. Epidemiol. 15, 17–28. http://dx.doi.org/10.1038/sj.jea.7500378.
Messer, L.C., Kaufman, J.S., Dole, N., Herring, A., Laraia, B.A., 2006. Violent crime exposure classification and adverse birth outcomes: a geographically-defined cohort study. Int. J. Health Geogr. 5, 22. http://dx.doi.org/10.1186/1476-072X-5-22.
Molitor, J., Jerrett, M., Chang, C.C., Molitor, N.T., Gauderman, J., Berhane, K., McConnell, R., Lurmann, F., Wu, J., Winer, A., Thomas, D., 2007. Assessing uncertainty in spatial exposure models for air pollution health effects assessment. Env. Health Perspect. 115, 1147–1153.
Molitor, J., Su, J.G., Molitor, N.-T., Rubio, V.G., Richardson, S., Hastie, D., Morello-Frosch, R., Jerrett, M., 2011. Identifying vulnerable populations through an examination of the association between multipollutant profiles and poverty. Environ. Sci. Technol. 45, 7754–7760. http://dx.doi.org/10.1021/es104017x.
Morello-Frosch, R., Shenassa, E.D., 2006. The environmental "Riskscape" and social inequality: implications for explaining maternal and child health disparities. Environ. Health Perspect. 114, 1150–1153. http://dx.doi.org/10.1289/ehp.8930.
Novák, J., Hilscherová, K., Landlová, L., Čupr, P., Kohút, L., Giesy, J.P., Klánová, J., 2014. Composition and effects of inhalable size fractions of atmospheric aerosols in the polluted atmosphere. Part II: in vitro biological potencies. Environ. Int. 63, 64–70. http://dx.doi.org/10.1016/j.envint.2013.10.013.
Padula, A.M., Mortimer, K., Hubbard, A., Lurmann, F., Jerrett, M., Tager, I.B., 2012. Exposure to traffic-related air pollution during pregnancy and term low birth weight: estimation of causal associations in a semiparametric model. Am. J. Epidemiol. 176, 815–824. http://dx.doi.org/10.1093/aje/kws148.
Parker, J.D., Rich, D.Q., Glinianaia, S.V., Leem, J.H., Wartenberg, D., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L., Gehring, U., Gouveia, N., Grillo, P., Ha, E., van den Hooven, E.H., Jalaludin, B., Jesdale, B.M., Lepeule, J., Morello-Frosch, R., Morgan, G.G., Slama, R., Pierik, F.H., Pesatori, A.C., Sathyanarayana, S., Seo, J., Strickland, M., Tamburic, L., Woodruff, T.J., 2011. The international collaboration on air pollution and pregnancy outcomes: initial results. Environ. Health Perspect. 119, 1023–1028. http://dx.doi.org/10.1289/ehp.1002725.
Pedersen, M., Gehring, U., Beelen, R., Wang, M., Giorgis-Allemand, L., Andersen, A. M.N., Basagaña, X., Bernard, C., Cirach, M., Forastiere, F., de Hoogh, K., Gražulevičienė, R., Gruzieva, O., Hoek, G., Jedynska, A., Klümper, C., Kooter, I.M., Krämer, U., Kukkonen, J., Porta, D., Postma, D.S., Raaschou-Nielsen, O., van Rossem, L., Sunyer, J., Sørensen, M., Tsai, M.-Y., Vrijkotte, T.G., Wilhelm, M., Nieuwenhuijsen, M.J., Pershagen, G., Brunekreef, B., Kogevinas, M., Slama, R., 2015. Elemental constituents of particulate matter and newborn's size in eight European cohorts. Environ. Health Perspect. . http://dx.doi.org/10.1289/ehp.1409546
Ponce, N.A., 2005. Preterm birth: the interaction of traffic-related air pollution with economic hardship in Los Angeles neighborhoods. Am. J. Epidemiol. 162, 140–148. http://dx.doi.org/10.1093/aje/kwi173.
Proietti, E., Röösli, M., Frey, U., Latzin, P., 2013. Air pollution during pregnancy and neonatal outcome: a review. J. Aerosol Med. Pulm. Drug Deliv. 26, 9–23. http://dx.doi.org/10.1089/jamp.2011.0932.
Ramachandran, G., Adgate, J.L., Pratt, G.C., Sexton, K., 2003. Characterizing Indoor and Outdoor 15 Minute Average PM 2.5 Concentrations in Urban Neighborhoods. Aerosol Sci. Technol. 37, 33–45. http://dx.doi.org/10.1080/02786820300889.
Reid, C., O'Neill, M., Gronlund, C., Brines, S., Brown, D., Diez-Roux, A., Schwartz, J., 2009. Mapping community determinants of heat vulnerability. Environ. Health Perspect. . http://dx.doi.org/10.1289/ehp.0900683
Ritz, B., Wilhelm, M., 2008. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin. Pharmacol. Toxicol. 102, 182–190. http://dx.doi.org/10.1111/j.1742-7843.2007.00161.x.
Ritz, B., Wilhelm, M., Hoggatt, K.J., Ghosh, J.K.C., 2007. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the university of California, Los Angeles. Am. J. Epidemiol. 166, 1045–1052. http://dx.doi.org/10.1093/aje/kwm181.
Rue, H., Martino, S., Chopin, N., 2009. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J. R. Stat. Soc. Ser. B Stat. Methodol. 71, 319–392. http://dx.doi.org/10.1111/j.1467-9868.2008.00700.x.
Rue, H., Martino, S., Lindgren, F., Simpson, D., Riebler, A., Krainski, E., 2015. INLA: Functions which allow to perform full Bayesian analysis of latent Gaussian models using Integrated Nested Laplace Approximaxion.
Rue, H., Martino, S., Lindgren, F., Simpson, D., Riebler, A., Krainski, E., 2014. Functions which allow to perform full Bayesian analysis of latent Gaussian models using Integrated Nested Laplace Approximaxion [WWW Document]. URL ⟨http://inla.googlecode.com/hg-history/default/rinla/DESCRIPTION⟩.
Samoli, E., Analitis, A., Touloumi, G., Schwartz, J., Anderson, H.R., Sunyer, J., Bisanti, L., Zmirou, D., Vonk, J.M., Pekkanen, J., Goodman, P., Paldy, A., Schindler, C., Katsouyanni, K., 2004. Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. Environ. Health Perspect. 113, 88–95. http://dx.doi.org/10.1289/ehp.7387.
Schempf, A., Strobino, D., O'Campo, P., 2009. Neighborhood effects on birthweight: an exploration of psychosocial and behavioral pathways in Baltimore, 1995–1996. Soc. Sci. Med. 68, 100–110. http://dx.doi.org/10.1016/j.socscimed.2008.10.006.
Shah, P.S., Balkhair, T., 2011. Air pollution and birth outcomes: a systematic review. Environ. Int. 37, 498–516. http://dx.doi.org/10.1016/j.envint.2010.10.009.
Shankardass, K., McConnell, R., Jerrett, M., Milam, J., Richardson, J., Berhane, K., 2009. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proc. Natl. Acad. Sci. USA 106, 12406–12411. http://dx.doi.org/10.1073/pnas.0812910106.
Singer, B.C., Harley, R.A., 2000. A fuel-based inventory of motor vehicle exhaust emissions in the Los Angeles area during summer 1997. Atmos. Environ. 34, 1783–1795. http://dx.doi.org/10.1016/S1352-2310(99)00358-1.
Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111. http://dx.doi.org/10.1016/j.envres.2012.05.007.
Su, J.G., Jerrett, M., Morello-Frosch, R., Jesdale, B.M., Kyle, A.D., 2012. Inequalities in cumulative environmental burdens among three urbanized counties in California. Environ. Int. 40, 79–87. http://dx.doi.org/10.1016/j.envint.2011.11.003.
Thompson, J.A., Bissett, W.T., Sweeney, A.M., 2014. Evaluating geostatistical modeling of exceedance probability as the first step in disease cluster investigations: very low birth weights near toxic Texas sites. Environ. Health Glob. Access Sci. Source 13, 47. http://dx.doi.org/10.1186/1476-069X-13-47.
Van Donkelaar, A., Martin, R.V., Brauer, M., Kahn, R., Levy, R., Verduzco, C., Villeneuve, P.J., 2010. Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. Environ. Health Perspect. 118, 847–855. http://dx.doi.org/10.1289/ehp.0901623.
Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2011. Traffic-related air toxics and term low birth weight in Los Angeles County, California. Environ. Health Perspect. 120, 132–138. http://dx.doi.org/10.1289/ehp.1103408.

Williams, B.L., Pennock-Román, M., Suen, H.K., Magsumbol, M.S., Ozdenerol, E., 2007. Assessing the impact of the local environment on birth outcomes: a case for HLM. J. Expo. Sci. Environ. Epidemiol. 17, 445–457. http://dx.doi.org/10.1038/sj.jes.7500537.

Wu, J., Wilhelm, M., Chung, J., Ritz, B., 2011. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ. Res. 111, 685–692. http://dx.doi.org/10.1016/j.envres.2011.03.008.

Zhuoqiong, He, Sun, Dongchu, 2000. Hierarchical Bayes estimation of hunting success rates with spatial correlations. Biometrics 56, 360–367. http://dx.doi.org/10.1111/j.0006-341X.2000.00360.x 360–7.