Association between Birthweight and Ambient $PM_{2.5}$ in United States: Individually-varied Susceptibility and Spatial Heterogeneity

Tao Xue[1], Ph.D; Tong Zhu[1,*], Ph.D; Yiqun Han[2] Ph.D

1 BIC-ESAT and SKL-ESPC, College of Environmental Science and Engineering, Peking University, Beijing 100871, China

2 Analytical, Environmental and Forensic Sciences, School of Population Health & Environmental Sciences, Kings College London, United Kingdom

* Corresponding to Dr. Zhu. Address: Room 501, College of Environmental Science and Engineering, Peking University, Beijing 100871, China; Telephone: 010-62754789; E-mail: tzhu@pku.edu.cn

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Abstract

The association between maternal exposure to $PM_{2.5}$ and birthweight varies geographically, which may be caused by susceptibility. Whether this population-level association is a function of mixtures of individuals with different susceptibilities is unclear. We investigated the probability distribution of individuals with different susceptibilities to $PM_{2.5}$-related birthweight change, and evaluated spatial variation of the effect across United States (US). We estimated the individual-level susceptibility using the effect of $PM_{2.5}$ among a homogenous subpopulation, which was defined by a specific combination of modifiers. According to frequencies for all combinations, we derived the probability distribution of differential susceptibilities across US and by states. From birth certificates across US (1999-2004), we analyzed a total of 18,317,707 samples of singletons. Of the samples, 54–55% were assigned valid exposures, and linked to $PM_{2.5}$. The subpopulation-specific associations of $PM_{2.5}$ on birthweight change (*i.e.*, susceptibilities) ranged from negative to positive. For the first-trimester exposure, 61.4% of the associations were negative, and the mean was -1.01 g (95% confidence interval, CI: -1.63, -0.38) of birthweight change per 5 $\mu g/m^3$ increase of $PM_{2.5}$. The state-level associations varied (from -2.04 g [-2.76, -1.31] in New Hampshire to -0.30 g [-1.01, 0.41] in Texas) with demographic compositions in US. The between-state variation of maternal race and education level were the greatest contributors to the spatial heterogeneity. Our findings may be useful to the policymaker in planning interventions for subpopulations susceptible to ambient pollution.

Keywords: Fine particulate matter; $PM_{2.5}$; birthweight; susceptibility; infant health

Introduction

Maternal exposure to ambient pollutants, including fine particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$), is associated with decreased birthweight and the incidence of low birthweight (LBW) (Dadvand *et al*. 2013; Ebisu and Bell 2012; Ebisu *et al*. 2016; Hao *et al*. 2016; Parker and Woodruff 2008; Pedersen *et al*. 2013; Stieb *et al*. 2016), a risk factor for infant morbidity and mortality and development of diseases during adulthood (McCormick 1985). However, these associations differ between studies (Dadvand *et al*. 2013; Sun *et al*. 2016) and vary geographically (Ebisu *et al*. 2016; Hao *et al*. 2016; Parker and Woodruff 2008). Few studies have assessed the reasons underlying this heterogeneity. The effect on birthweight of a given ambient $PM_{2.5}$ level varies among subpopulations; *e.g.*, different ethnicities (Ebisu and Bell 2012); this is termed differential susceptibility to $PM_{2.5}$ (Bell *et al*. 2013; Sacks *et al*. 2011). The fraction of susceptible individuals in the surveyed population varies among studies and geographically. Thus, a comprehensive evaluation of individual variations in susceptibility to $PM_{2.5}$ is warranted.

The terms *susceptibility*, *vulnerability*, and *sensitivity* are used interchangeably to denote inter-individual variation in the risk of adverse health outcomes per unit increment in ambient exposure to pollutants (Bell *et al*. 2013). Regardless of the subtle distinctions among these terms, in this study we use *susceptibility* to represent the magnitude of toxicity of air pollution to an individual. Susceptibility is dependent on internal factors (*e.g.*, genetics and underlying disease[s]), external factors (*e.g.*, socioeconomic status), and exposure patterns (*e.g.*, travel). Epidemiological studies use the term 'effect-modifier' to denote these factors or their surrogates, and subject them to interaction analyses. However, previous studies explored single effect-modifiers separately. For example, the $PM_{2.5}$-LBW association is reportedly stronger among white mothers (Ebisu and Bell 2012). The simplicity of such studies may preclude evaluation of the different levels of susceptibility among the general population. Previous studies have reported three-way (Dubowsky *et al*. 2006) or higher-order interactions (Rosa *et al*. 2017) between the health effects of $PM_{2.5}$ and individual characteristics, which indicates that multiple effect-modifiers might contribute to susceptibility both cumulatively and dependently. Additionally, few previous studies quantified the fraction of susceptible individuals among the general population, which is determined by not only the modifying

effects of individual characteristics but also their joint probability distribution among the target population.

To fully characterize susceptibility to $PM_{2.5}$, we assume that the individual-specific health effect is determined by multiple effect-modifiers; thus, susceptibility may be quantified as a function of multiple variables at the level of the individual. Therefore, individuals with identical effect-modifiers have identical susceptibilities. In other words, the individual-specific effect (*i.e.*, susceptibility) can be estimated from a homogenous subpopulation. For the $PM_{2.5}$-related birthweight change, we collected 11 infant and maternal variables as effect-modifiers or their surrogates to represent the gradient variation of individual-specific susceptibilities. These variables were selected according to previous findings and data availability, and are described in the following section. In this study, we quantify the individual-specific magnitudes of susceptibility as the birthweight change per unit increment of $PM_{2.5}$, which are estimated in homogenous subgroups categorized by the 11 variables. By combining the different susceptibilities with the probabilities of the corresponding subgroups, we derived a new statistical measure, the 'human susceptibility distribution', which reflects both the magnitude and the prevalence of susceptibility in the general population.

Although several studies have linked nationwide data of birthweight or LBW to ambient particles (*e.g.*, $PM_{2.5}$ [Hao *et al*. 2016; Parker and Woodruff 2008], $PM_{2.5}$ [Ebisu and Bell 2012], $PM_{2.5–10}$ [Ebisu *et al*. 2016], and PM_{10} [Parker and Woodruff 2008]) in the United States (US), none explored susceptibility to the effect of $PM_{2.5}$. Using US birth certificates and the $PM_{2.5}$ concentrations monitored by national networks, we derived the human susceptibility distribution of the $PM_{2.5}$-related change in birthweight. Furthermore, by considering geographic variation in the proportions of susceptible individuals in the US, we assessed the spatial variation of $PM_{2.5}$-related birthweight change as a practical application of the human susceptibility distribution.

METHODS

Study population

Birth certificate data of the contiguous US from 1999 to 2004 were obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention. This database was in

previous studies on the adverse effects of air pollutants on infants (*e.g.*, Hao *et al*. 2016). Many individual-level variables on both newborns and their mothers, such as county of residence, date of last menstrual period (LMP), and birthweight, were available during 1999–2004. Because many population characteristics could affect the susceptibility to $PM_{2.5}$-related birthweight change, we targeted the 11 individual characteristics (Table 1) used as the modeling covariates in previous studies (Ebisu and Bell 2012; Ebisu *et al*. 2016).

We prepared the birth data as described previously (Ebisu and Bell 2012; Ebisu *et al*. 2016). Briefly, we first excluded plural deliveries, as the target population was singleton births. Second, we assumed that the pregnancy period began 2 weeks after the LMP and was equal to the reported gestational duration. The reported month of birthdate was used to validate the estimated gestational period. We excluded birth records when the difference between the estimated delivery date and the middle day of the birth month was more than 30 days. Third, based on a previous study (Alexander *et al*. 1996), we excluded records with impossible combinations of gestational age and birthweight. Fourth, we excluded records with missing values for any of the 11 individual characteristics. All births from California were removed because maternal status on smoking or tobacco usage was not recorded on California birth certificates. After applying the above exclusion criteria, 18,317,707 records were analyzed (Web Figure 1).

Table 1. Characteristics of the Study Population.

Characteristic		Singleton births* n (%)	Valid records# n (%)	Regression samples assigned with environmental exposures†, n (%)			
				Entire pregnancy	first trimester	second trimester	third trimester
Total		23,354,466 (100.0%)	18,317,707 (100.0%)	10,043,330 (100.0%)	9,810,885 (100.0%)	10,256,781 (100.0%)	10,681,193 (100.0%)
Infant sex	Female	11,398,186 (48.8%)	8,945,471 (48.8%)	4,906,406 (48.9%)	4,792,308 (48.8%)	5,010,150 (48.8%)	5,217,436 (48.8%)
	Male	11,956,280 (51.2%)	9,372,236 (51.2%)	5,136,924 (51.1%)	5,018,577 (51.2%)	5,246,631 (51.2%)	5,463,757 (51.2%)

Maternal age	< 20 years	2,636,792 (11.3%)	2,099,741 (11.5%)	990,447 (9.9%)	965,597 (9.8%)	1,013,757 (9.9%)	1,058,656 (9.9%)
	20–34 years	17,578,360 (75.3%)	13,850,271 (75.6%)	7,594,105 (75.6%)	7,419,332 (75.6%)	7,754,704 (75.6%)	8,075,441 (75.6%)
	> 35 years	3,139,314 (13.4%)	2,367,695 (12.9%)	1,458,778 (14.5%)	1,425,956 (14.5%)	1,488,320 (14.5%)	1,547,096 (14.5%)
Maternal race	Black	2,044,869 (8.8%)	1,479,205 (8.1%)	956,270 (9.5%)	945,799 (9.6%)	965,066 (9.4%)	982,654 (9.2%)
	White	18,474,953 (79.1%)	14,478,758 (79.0%)	7,743,464 (77.1%)	7,564,698 (77.1%)	7,911,310 (77.1%)	8,245,458 (77.2%)
	Other	2,834,644 (12.1%)	2,359,744 (12.9%)	1,343,596 (13.4%)	1,300,388 (13.3%)	1,380,405 (13.5%)	1,453,081 (13.6%)
Maternal marital status	Single	8,003,728 (34.3%)	6,231,196 (34.0%)	3,281,936 (32.7%)	3,208,356 (32.7%)	3,347,524 (32.6%)	3,475,010 (32.5%)
	Married	15,350,738 (65.7%)	12,086,511 (66.0%)	6,761,394 (67.3%)	6,602,529 (67.3%)	6,909,257 (67.4%)	7,206,183 (67.5%)
Maternal education	< 12 years	4,865,385 (20.8%)	3,793,769 (20.7%)	1,952,270 (19.4%)	1,909,574 (19.5%)	1,992,583 (19.4%)	2,069,272 (19.4%)
	12 years	6,903,795 (29.6%)	5,787,527 (31.6%)	2,919,091 (29.1%)	2,847,758 (29.0%)	2,984,003 (29.1%)	3,110,364 (29.1%)
	> 12 years	10,315,406 (44.2%)	8,736,411 (47.7%)	5,171,969 (51.5%)	5,053,553 (51.5%)	5,280,195 (51.5%)	5,501,557 (51.5%)
	Unknown	1,269,880 (5.4%)					
Gestational length	< 37 weeks (Preterm)	2,411,467 (10.3%)	1,926,845 (10.5%)	995,822 (9.9%)	977,022 (10.0%)	1,019,312 (9.9%)	1,050,878 (9.8%)
	37–42 weeks (Term)	19,090,032 (81.7%)	15,114,977 (82.5%)	8,388,623 (83.5%)	8,194,244 (83.5%)	8,565,132 (83.5%)	8,923,736 (83.5%)

	> 42 weeks (Postmature)	1,608,097 (6.9%)	1,275,885 (7.0%)	658,885 (6.6%)	639,619 (6.5%)	672,337 (6.6%)	706,579 (6.6%)
	Unknown	244,870 (1.0%)					
Parity	Parous	15,458,525 (66.2%)	12,227,065 (66.7%)	6,678,689 (66.5%)	6,524,152 (66.5%)	6,821,003 (66.5%)	7,103,211 (66.5%)
	Nulliparous	7,792,114 (33.4%)	6,090,642 (33.3%)	3,364,641 (33.5%)	3,286,733 (33.5%)	3,435,778 (33.5%)	3,577,982 (33.5%)
	Unknown	103,827 (0.4%)					
Prenatal care	After first trimester (or no care)	3,636,113 (15.6%)	3,071,801 (16.8%)	1,561,662 (15.5%)	1,523,712 (15.5%)	1,593,009 (15.5%)	1,655,510 (15.5%)
	From first trimester	18,265,229 (78.2%)	15,245,906 (83.2%)	8,481,668 (84.5%)	8,287,173 (84.5%)	8,663,772 (84.5%)	9,025,683 (84.5%)
	Unknown	1,453,124 (6.2%)					
Delivery method	C-section	5,589,483 (23.9%)	4,375,312 (23.9%)	2,440,006 (24.3%)	2,392,339 (24.4%)	2,483,989 (24.2%)	2,569,356 (24.1%)
	Vaginal	17,615,352 (75.4%)	13,942,395 (76.1%)	7,603,324 (75.7%)	7,418,546 (75.6%)	7,772,792 (75.8%)	8,111,837 (75.9%)
	Unknown	149,631 (0.6%)					
Maternal tobacco use during pregnancy	No	16,896,188 (72.3%)	16,190,222 (88.4%)	9,142,241 (91.0%)	8,934,333 (91.1%)	9,332,899 (91.0%)	9,713,762 (90.9%)
	Yes	2,229,109 (9.5%)	2,127,485 (11.6%)	901,089 (9.0%)	876,552 (8.9%)	923,882 (9.0%)	967,431 (9.1%)
	Unknown	4,229,169 (18.1%)					

Maternal alcohol use during pregnancy	No	18,929,977 (81.1%)	18,163,924 (99.2%)	9,966,643 (99.2%)	9,736,122 (99.2%)	10,178,077 (99.2%)	10,598,766 (99.2%)
	Yes	163,802 (0.7%)	153,783 (0.8%)	76,687 (0.8%)	74,763 (0.8%)	78,704 (0.8%)	82,427 (0.8%)
	Unknown	4,260,687 (18.2%)					

* The target population.

The samples used to calculate prevalence of susceptible individuals.

† The samples used to derive individual-level susceptibility.

Statistics of the non-valid samples or valid samples that were excluded from regressions samples can be derived by column* - column# or column# - column†, respectively. Such statistics are not displayed here.

Exposure assessment

Daily values of $PM_{2.5}$ from January 1998 to December 2004 were obtained from the US Environmental Protection Agency Air Quality System network (Web Figure 1). We first assigned and averaged the monitored $PM_{2.5}$ levels by county, and prepared the exposure values during the entire pregnancy and each of the three trimesters (first trimester, 1–13 weeks; second trimester, 14–26 weeks; and third trimester, 27 weeks to delivery) as described previously (Ebisu and Bell 2012). Briefly, we first calculated weekly averages and then derived the exposure value during the entire pregnancy or each trimester based on the estimated period of pregnancy for each birth, if more than 75% of the weekly values were available. We obtained temperature data from January 1998 to December 2004 from the National Climatic Data Center, and transformed the weekly averages of monitored temperature into county-level averages during the entire pregnancy or each trimester, analogously.

Statistical analysis

The statistical analysis procedure is shown in Figure 1. Briefly, among all birth records, those assigned with environmental exposures ($PM_{2.5}$ and temperature) were used as regression samples to link birthweight to maternal exposure to $PM_{2.5}$. We used a batch of separate regressions to derive subpopulation-specific susceptibilities. We also used all valid records to

estimate the frequencies of the subpopulations among the total study population. The two results were combined to estimate the human susceptibility distribution.

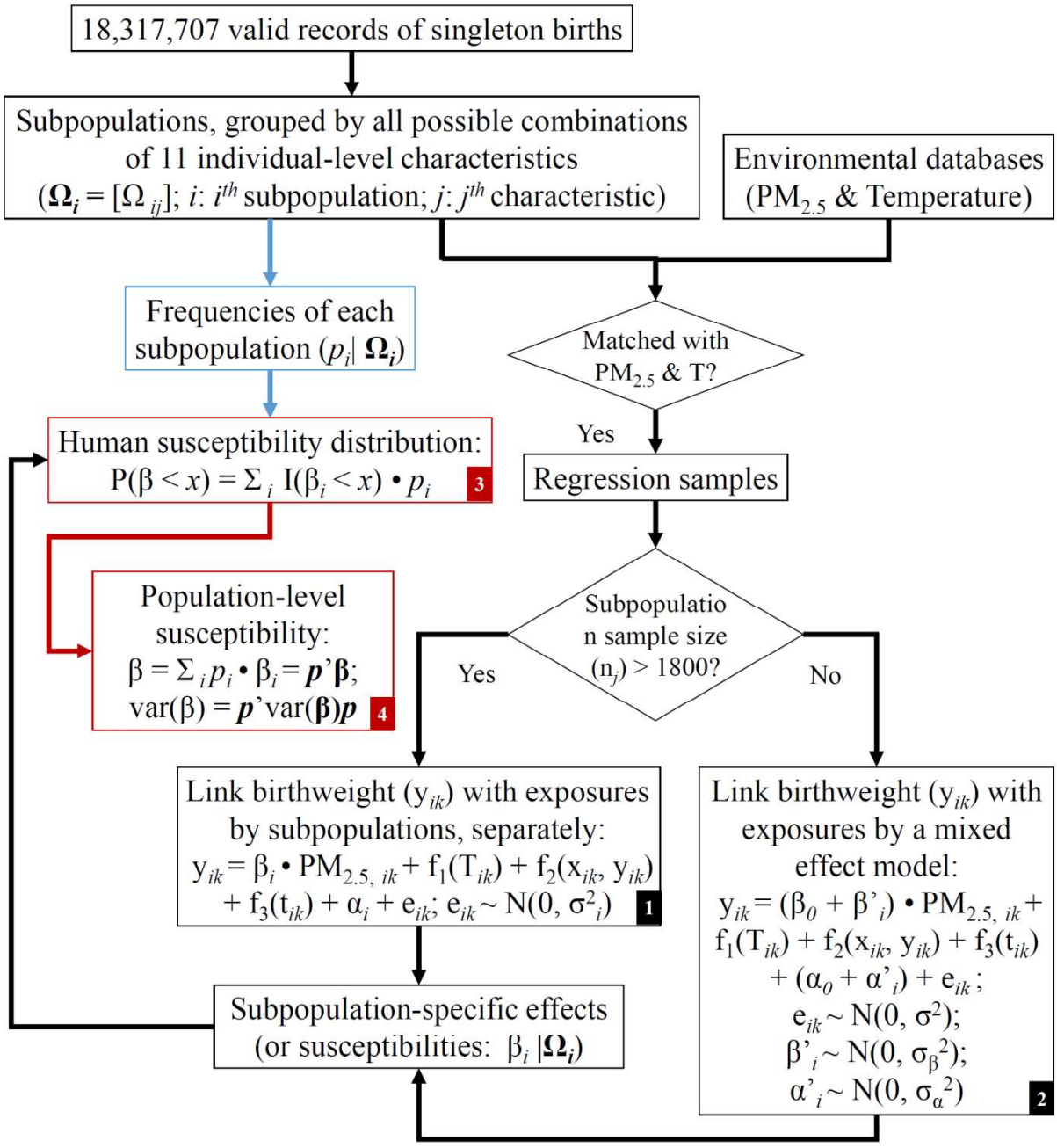

Figure 1. Statistical Analysis Procedure. Numbers (1–4) denote the equation indices. Black boxes show the derivation of subpopulation-specific susceptibilities; the blue box shows calculation of the frequency of each subpopulation; red boxes show the development and application of the susceptibility distribution.

First, we generated subpopulation indexes (i) based on 10,368 ($2^7 \times 3^4$) combinations of the population characteristics ($\mathbf{\Omega}_i$), which included 7 binary and 4 trinary variables. Among

them, 8,632 were present in the population according to valid records of singleton births. Only a portion of the valid birth certificates (those used as regression samples) could be simultaneously assigned levels of exposure to both $PM_{2.5}$ and temperature, due to the incomplete spatiotemporal coverage of the monitoring networks. The sample sizes are summarized in Table 1.

We next attempted to link birthweight to maternal exposure to $PM_{2.5}$ during the entire pregnancy and each trimester, independently within each subpopulation, with adjustments for three spline terms to control for the nonlinear confounding effects of temperature, the centroid coordinates of county of residence, and the temporal index (Figure 1: Equation 1). To model seasonality, 4 degrees of freedom per year were utilized in the spline term of temporal index. For some subpopulations, the regression sample size (n_i) might be too small to generate a robust estimate of the effect of $PM_{2.5}$. The statistical power of the regression model (Figure 1: Equation 1) increased to > 0.8 at a significance level of 0.05 when the sample size was > 1800 (Web Figure 2). Therefore, we combined the subpopulations with sample sizes < 1800, and estimated the subpopulation-specific effects using a mixed-effects model with a random slope and a random intercept (Figure 1: Equation 2). In this model, the subpopulation-specific effects ($\beta_0 + \beta'_i$) were assumed to be normally distributed with a mean value of β_0 and a standard deviation of σ_β^2. By combining the results of Equations 1 and 2, we derived the subpopulation-specific effects, which were used to quantify the variation in susceptibility according to the population characteristics ($\beta_i \mid \mathbf{\Omega}_i$).

Next, we approximated the probability that an individual belonged to a specific subpopulation ($p_i \mid \mathbf{\Omega}_i$) using the frequency of the subpopulation among all valid records of births. By considering the probability distribution of subpopulations ($p_i \mid \mathbf{\Omega}_i$) and the susceptibilities of these subpopulations to the $PM_{2.5}$-related birthweight change ($\beta_i \mid \mathbf{\Omega}_i$), we assessed the human susceptibility distribution for maternal exposure during the entire pregnancy and each trimester according to Equation 3 (Figure 1).

Finally, we calculated the average susceptibility and its variance at the population level (Figure 1: Equation 4). We applied the approach to quantify population susceptibility to $PM_{2.5}$-related birthweight change at the state level, and evaluated its spatial variation due to geographic differences in population composition.

In sensitivity analyses, we derived the susceptibility distribution based on two different samples. First, through excluding variables on usage of alcohol and tobacco from the set of 11 effect-modifiers, we included California births into our valid sample and regression samples and, re-estimated the susceptibility distribution based on 9 variables. Second, assuming the individual-level susceptibility also varies geographically, we incorporated an indicator for four US regions (Web Figure 1) as the additional effect-modifier, and re-estimated the susceptibility distribution based on 12 variables.

All statistical analyses were performed in R version 3.4.1 (R Core Team 2017). The mixed-effect models was conducted using the *lme4* package (Bates *et al*. 2014). The power curve was calculated using the *pwr* package (Champely 2017). The statistical significance level was set at 0.05.

RESULTS

Descriptive statistics

During the study period, there were 24,135,665 births in the contiguous U.S., and 23,354,466 of them were singletons. After exclusions, the study dataset comprised 18,317,707 valid records of singleton births. Among them, 54–55% (about 10 million, Table 1) that were assigned valid environmental exposures (both $PM_{2.5}$ and temperature) during the whole pregnancy or one trimester were subjected to regression analysis of birthweight. The spatial distribution of the infants is shown in Web Figure 1, together with the $PM_{2.5}$-monitoring locations. California was excluded from the main analysis, because maternal use of alcohol or tobacco was not reported there during the study period. The regression samples covered most other populous areas.

The infant and maternal characteristics for (1) all singleton births, (2) valid records after application of the exclusion criteria, and (3) regression samples are summarized in Table 1. The three types of samples were similar in most of the characteristics, which suggested that the exclusions did not considerably change the demographic composition of the study population. The regression samples had a slightly higher fraction of births with a maternal education level of > 12 years (51.5% vs. 47.7%), because these tended to be from urban or suburban areas. The summary statistics for the continuous variables (*i.e.*, birthweight, $PM_{2.5}$, and temperature) are

presented in Table 2. The mean birthweight was 3.34 kg, and the mean $PM_{2.5}$ level was 13.1 $\mu g/m^3$. The continuous variables were similarly distributed in all the regression datasets.

Table 2. Statistical Summary of the Continuous Variables in the Regression Analysis Datasets.

Period	Variable	Mean	Standard deviation	Quantiles				
				2.5%	25%	50%	75%	97.5%
Entire pregnancy	Birthweight (g)	3342	542	2155	3033	3360	3686	4350
	$PM_{2.5}$ $\mu g/m^3$	13.1	2.9	7.4	11.1	13.1	15.1	18.6
	Temperature (°C)	14.1	5.3	5.0	10.1	13.6	17.9	24.5
First trimester	Birthweight (g)	3341	542	2155	3033	3358	3686	4345
	$PM_{2.5}$ $\mu g/m^3$	13.1	3.5	6.8	10.7	13	15.4	20.4
	Temperature (°C)	13.6	8.8	−2.7	6.6	14.3	20.9	27.9
Second trimester	Birthweight (g)	3342	542	2155	3033	3360	3686	4350
	$PM_{2.5}$ $\mu g/m^3$	13.1	3.5	6.7	10.7	12.9	15.4	20.3
	Temperature (°C)	14.1	8.8	−2.6	7.1	15.0	21.3	28.0
Third trimester	Birthweight (g)	3343	541	2155	3033	3365	3686	4355
	$PM_{2.5}$ $\mu g/m^3$	13.1	3.5	6.7	10.7	12.9	15.3	20.2
	Temperature (°C)	14.4	8.6	−2.2	7.8	15.5	21.3	28.0

Individual-specific susceptibility

The characteristics and regression results of the largest 10 subpopulations (Tables 3-4; ID: 1-10) are shown in Tables 3-4. None of these groups had a sample size of < 140,000 for regression analyses. Within each subpopulation, all births were identical in terms of the 11 individual-level characteristics, suggesting that they represented a specific type of individual. Among the 10 groups, birthweight reduction was significantly associated with maternal exposure to $PM_{2.5}$ during the entire pregnancy or one trimester for IDs 2, 3, 7, 8 and 10, and no significantly positive association was found. For the largest subpopulation (ID 1), each 5 $\mu g/m^3$ increment of $PM_{2.5}$ was weakly associated with a decrease in birthweight of 0.61 g (-1.86, 3.08) or 1.76 g (-0.63, 4.15) during the first or second trimester, respectively. For the second-largest subpopulation (ID 2), which differed from the ID 1 group only in sex (female vs. male), the

$PM_{2.5}$ level was significantly associated with decreased birthweight during the entire pregnancy and the first two trimesters. The association was significantly stronger in the ID 2 subpopulation than the ID1 subpopulation.

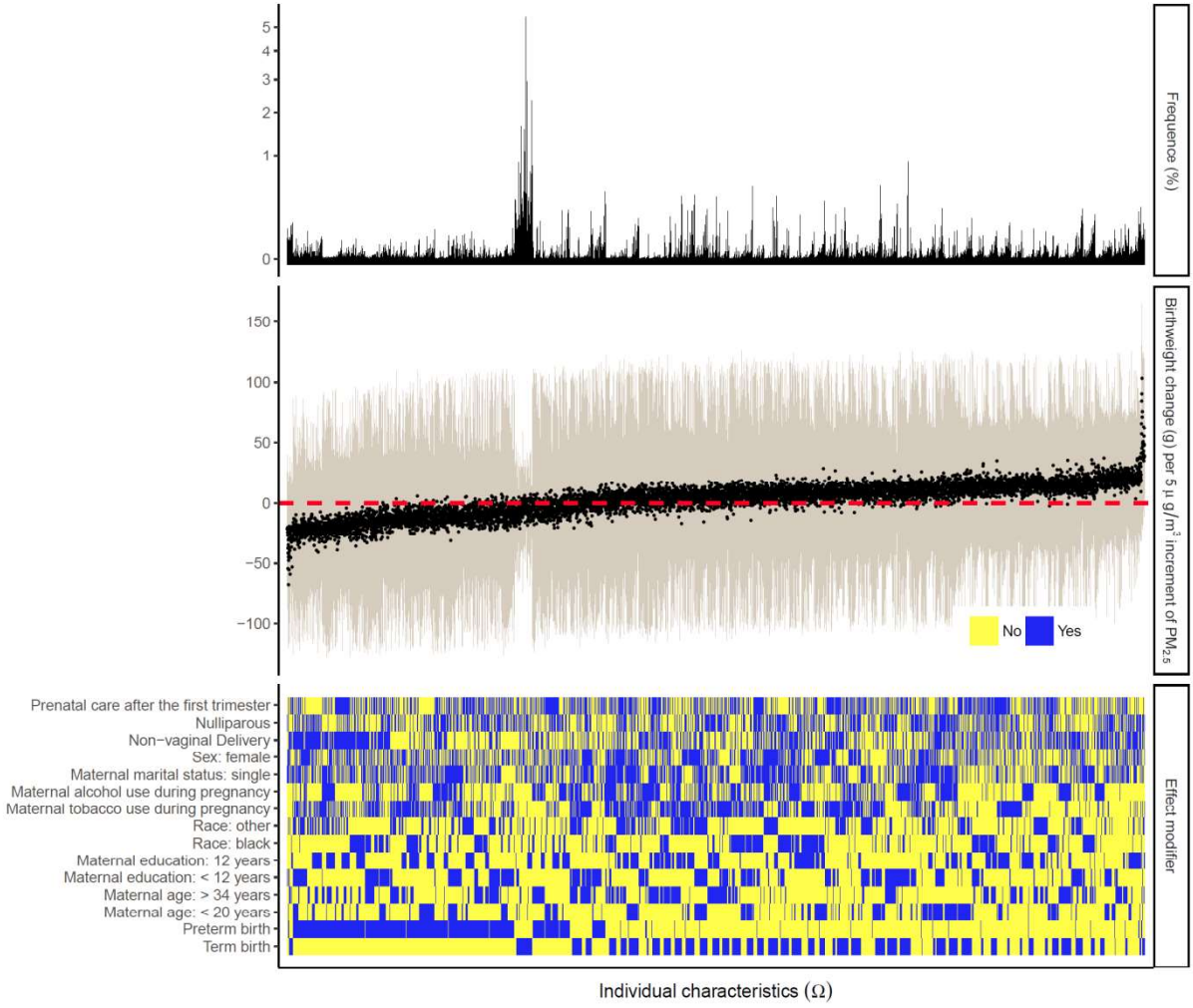

Figure 2. Estimated Effects (middle panel) of Maternal Exposure to $PM_{2.5}$ during the First Trimester on Birthweight in all Subpopulations, Classified According to Combinations of Individual-level Effect-modifiers (bottom panel), with the Probability Distribution (top panel) of those Subpopulations in the Contiguous US. The Order of Combinations is Determined Using a Clustering Method, Which Tends to Put Individuals with Similar Characteristics and Susceptibility Together.

The estimated effects from the subpopulation-specific regressions, together with their frequencies, are shown in Figure 2 (first trimester) and Web Figures 3–5 (second trimester, third trimester, and entire pregnancy). The associations between maternal exposure to $PM_{2.5}$

and birthweight change varied markedly according to the combinations of individual characteristics, and the associations were negative for most of the populous subgroups (frequency > 1%). Because the individuals within a subpopulation are homogenous, the variable effects reflect the gradient variation of individual susceptibilities to $PM_{2.5}$ among the general population.

Table 3. Characteristics for the largest 10 subpopulations.

ID	Infant sex	Maternal age	Maternal education	Parity	Delivery method	Other variables
1	Male	20-34 years	> 12 years	Parous	Vaginal	
2	Female	20-34 years	> 12 years	Parous	Vaginal	
3	Female	20-34 years	> 12 years	Nulliparous	Vaginal	Maternal race: White; Maternal marital status: Married; Gestational length: Term; Prenatal care: From first trimester; Maternal tobacco use during pregnancy: No; Maternal alcohol use during pregnancy: No.
4	Male	20-34 years	> 12 years	Nulliparous	Vaginal	
5	Male	20-34 years	12 years	Parous	Vaginal	
6	Female	20-34 years	12 years	Parous	Vaginal	
7	Male	> 35 years	> 12 years	Parous	Vaginal	
8	Female	> 35 years	> 12 years	Parous	Vaginal	
9	Male	20-34 years	> 12 years	Parous	C-section	
10	Female	20-34 years	> 12 years	Parous	C-section	

Table 4 Birthweight-$PM_{2.5}$ Associations for the Largest 10 Subpopulations. Significant effects are shown in bold in the bottom table ($P < 0.05$).

ID	Counts of valid records (percentage)	Birthweight change (g) per 5 μg/m^3 increment of $PM_{2.5}$ (95% CI)			
		Entire pregnancy	first trimester	second trimester	third trimester
1	996,906 (5.4%)	1.38 (-2.40, 5.15)	-0.61 (-3.08, 1.86)	-1.76 (-4.15, 0.63)	1.51 (-0.93, 3.96)
2	971,410 (5.3%)	**-4.24 (-7.95, -0.54)**	**-4.34 (-6.76, -1.92)**	**-3.63 (-5.98, -1.28)**	0.38 (-2.02, 2.77)
3	540,797 (3.0%)	-1.97 (-6.76, 2.81)	**-4.57 (-7.72, -1.42)**	-1.66 (-4.73, 1.40)	1.89 (-1.24, 5.02)
4	539,895 (2.9%)	0.95 (-4.04, 5.94)	-3.19 (-6.48, 0.10)	-1.61 (-4.81, 1.59)	3.45 (-0.19, 6.72)
5	433,877 (2.4%)	0.54 (-5.39, 6.46)	-0.88 (-4.81, 3.04)	-1.58 (-5.44, 2.27)	2.93 (-0.97, 6.83)
6	424,114 (2.3%)	2.59 (-3.16, 8.34)	0.32 (-3.53, 4.18)	-3.01 (-6.77, 0.76)	2.82 (-0.99, 6.63)
7	300,864 (1.6%)	**-9.51 (-16.44, -2.57)**	**-7.42 (-12.04, -2.80)**	**-6.73 (-11.21, -2.25)**	-1.44 (-5.99, 3.12)
8	296,404 (1.6%)	**-9.47 (-16.22, -2.72)**	**-7.92 (-12.40, -3.44)**	**-7.51 (-11.86, -3.15)**	-0.46 (-4.94, 4.02)
9	286,518 (1.6%)	-5.19 (-13.02, 2.65)	-0.12 (-5.36, 5.12)	-5.07 (-10.23, 0.08)	-2.70 (-7.94, 2.54)
10	259,646 (1.4%)	**-9.72 (-17.61, -1.84)**	0.53 (-4.79, 5.84)	**-5.68 (-10.91, -0.46)**	**-8.49 (-13.78, -3.21)**

Susceptibility probability distribution

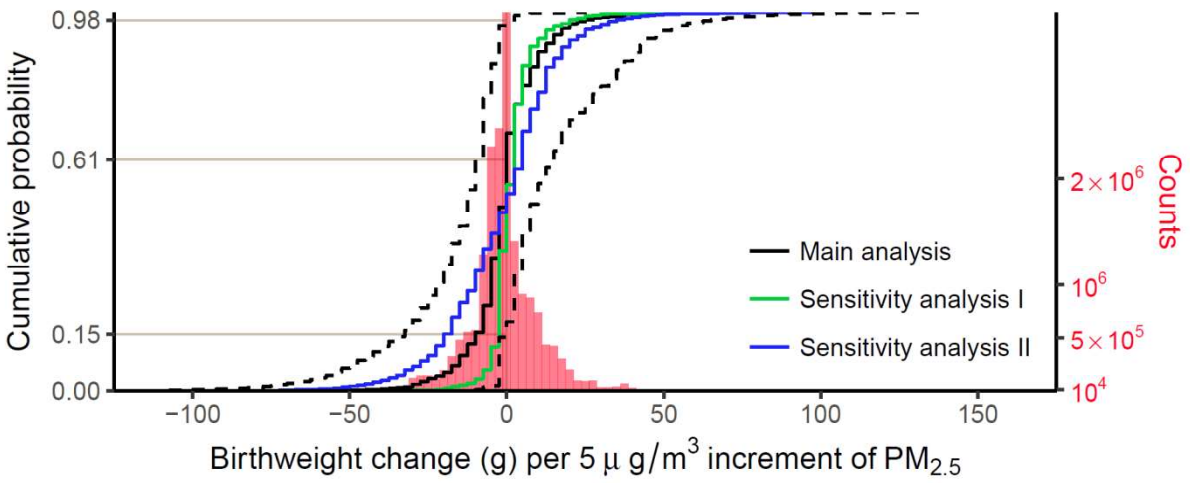

Figure 3. Probability Distribution for Susceptibility to Birthweight Change Related to Maternal Exposure to $PM_{2.5}$ during the First Trimester for Singleton Births in the Contiguous US. The Green and Blue Solid Lines Present the Estimated Cumulative Probability Functions in Sensitive Analyses. Sensitivity Analysis I: Inclusion of California Births and Exclusion of Alcohol/Tobacco Use in the Set of Effect-modifiers; Sensitivity Analysis II: Inclusion of the Regional Indicator in the Set of Effect-modifiers.

By combining the susceptibilities to $PM_{2.5}$ with the probability distribution of individuals, we derived the susceptibility distribution of the $PM_{2.5}$-related birthweight changes for singleton births in the contiguous US (Figure 3 [first trimester] and Web Figures 6–8 [second trimester, third trimester, and entire pregnancy]). The susceptibility distribution was centered close to zero. The median effects were 0.54, -0.89, -1.76, and 1.51 g changes in birthweight per 5 $\mu g/m^3$ increment of $PM_{2.5}$ during the entire pregnancy and the first, second, and third trimesters, respectively (Table 5). There were more statistically negative effects than statistically positive ones (Table 5). Particularly, the effects were negative for more than 50% of the births for exposure for maternal exposure during the first (61.4%) and second (65.4%) trimesters. The distributional susceptibilities suggested that each increment in maternal exposure to $PM_{2.5}$, especially during the first two trimesters, was likely to lead to a reduced birthweight, which is consistent with previous reports.

Table 5. Summary Statistics for the Distributions of the Estimated Effects of $PM_{2.5}$ on Birthweight by Subpopulation in the Contiguous US.

Statistics	Effect: birthweight change (g) per 5 μg/m^3 increment of $PM_{2.5}$			
	Entire pregnancy	First trimester	Second trimester	Third trimester
2.5% quantile	-28.98 (-75.14, 17.17)	-26.26 (-99.97, 47.45)	-24.29 (-53.12, 4.54)	-20.65 (-66.34, 25.05)
25% quantile	-7.00 (-16.70, 2.71)	-4.58 (-26.35, 17.18)	-5.68 (-10.91, -0.46)	-2.71 (-78.37, 72.96)
50% quantile	0.54 (-5.39, 6.46)	-0.89 (-91.51, 89.73)	-1.76 (-4.15, 0.63)	1.51 (-56.34, 59.37)
75% quantile	10.75 (1.49, 20.01)	3.53 (-23.71, 30.76)	3.36 (-39.04, 45.76)	6.30 (-79.17, 91.76)
97.5% quantile	45.08 (-2.56, 92.73)	23.05 (-6.72, 52.82)	26.36 (-18.23, 70.95)	26.90 (-27.38, 81.17)
Negative effect (%)	47.0%	61.4%	65.4%	38.3%
Significantly negative effect (%)	12.5%	14.8%	12.5%	3.6%
Significantly positive effect (%)	5.3%	2.2%	2.3%	6.8%

Population-level susceptibility: the weighted average

We quantified the average effect of $PM_{2.5}$ on birthweight within a target population (defined as population-level susceptibility) as the probability-weighted mean of the individual susceptibilities. The target populations were all singleton births in the contiguous US and subsets thereof (*e.g.*, all female births or births in a specific state). Web Table shows the population-level susceptibilities for our study population and of subsets defined by single individual-level factors. More description in the Web Appendix.

Spatial variation of state-level susceptibility

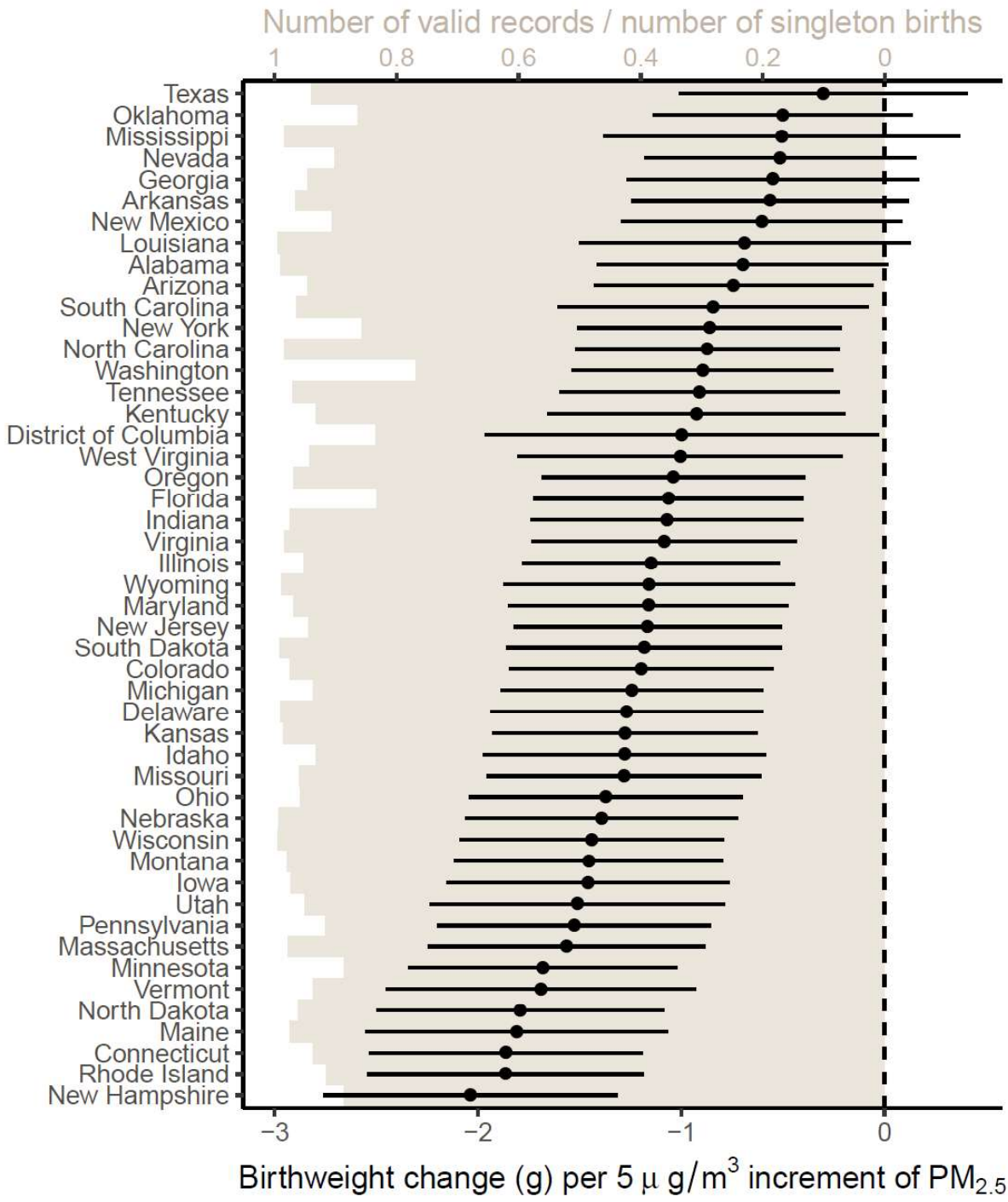

Figure 4. Spatial Variation of Susceptibility to Birthweight Change Related to Maternal Exposure to $PM_{2.5}$ during the First Trimester. The gray bar presents a ratio of the number of valid records against the number of singleton births (i.e., target population) in each county.

The level of susceptibility to the $PM_{2.5}$-related birthweight change varied markedly across the contiguous US (Figure 4 and Web Figure 9). All state-level susceptibilities to first-trimester exposure were significantly negative, except for some southern states (Figure 4). The effect of

each 5 μg/m^3 increment in $PM_{2.5}$ was associated with a 2.04 g (1.31, 2.76) reduction in birthweight in New Hampshire, and a 0.30 g (-0.41, 1.01) reduction in birthweight in Texas. Births in New England (New Hampshire, Connecticut, Maine, Vermont, Rhode Island and Massachusetts), some Midwestern states (Iowa, North Dakota and Minnesota), Utah, and Pennsylvania were more susceptible to $PM_{2.5}$-related reductions in birthweight. The spatial patterns of susceptibilities to $PM_{2.5}$ exposure during the entire pregnancy and other trimesters were similar (Web Figure 9). The spatial heterogeneity in the $PM_{2.5}$–birthweight association could be attributed to various combinations of effect-modifiers. Some modifiers (*e.g.*, infant sex) exerted considerable effects on the $PM_{2.5}$–birthweight association (Web Table), but contributed little to the spatial heterogeneity because they were evenly distributed among the states. Based on our findings, most of the variance in state-level susceptibility was due to maternal ethnicity or education level (Figure 5). The method used to quantify the contributions of the modifiers to the spatial variance of state-level susceptibility is detailed in the Web Appendix.

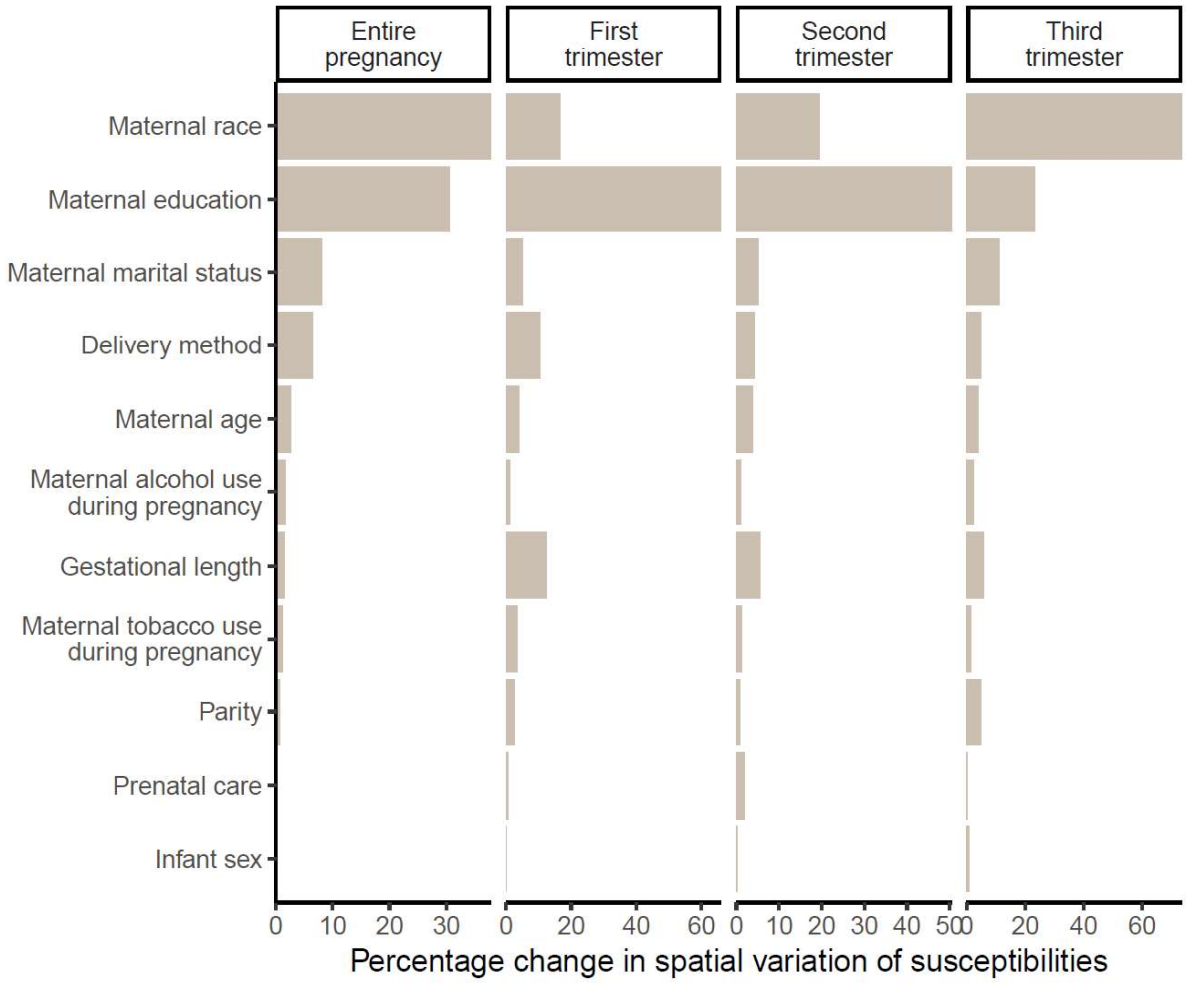

Figure 5. Contributions of the 11 Population Characteristics to the Spatial Variance of State-level Susceptibility.

Sensitivity analysis

In above analyses, we assumed that individual-level susceptibilities could be represented by the 11 individual-level effect-modifiers, which might be violated. In sensitivity analyses, we explored how the susceptibility distribution changed with different sets of effect-modifiers (Figure 3). Regardless of removing the variables of alcohol and tobacco usage from, or adding the regional indicator into the set of susceptibility-depended factors, there is no statistical difference between the estimated distributions (i.e., for a given level of susceptibility, Figure 3 shows no significant difference between the cumulative probabilities estimated from the three methods). However, the variance of the distributions tends to increase with the number of susceptibility-depended variables. For instance, in the second sensitivity analysis, after incorporating the geographic indicator, the susceptibility distribution becomes dispersed,

which suggests that some spatially-varying factors unmeasured in this study may also contribute to the variation of susceptibility. Such factors can belong to population characteristics like the 11 effect-modifiers or to other aspects, such as chemical components of $PM_{2.5}$. Because this study is focused on the explainable susceptibility that depends on individual-level variables rather than other aspects, the results are interpreted based on the model without the geographic indicator.

DISCUSSION

Unlike traditional studies, which associated maternal ambient exposure to birthweight after adjusting for several covariates, we regressed birthweight with $PM_{2.5}$ independently within different subpopulations. Using birth certificates, we estimated individual susceptibility to $PM_{2.5}$-related birthweight change according to type of birth in the contiguous US, and determined for the first time the susceptibility distribution in the general population.

The effect of maternal exposure to $PM_{2.5}$ on birthweight varied among individuals from negative to positive, and was not statistically significant for most of the study population (*i.e.*, 82.20% 83.00% 85.20% 89.60% for exposure during the entire pregnancy and the first, second, and third trimesters, respectively). However, the effect had a higher probability of being significantly negative (Table 5). Such variation of the effect is consistent with previous reports. Parker and Woodruff (2008) linked birthweight to 9-month exposure to $PM_{2.5}$ among singleton births delivered at 40 weeks of gestation in the US, and reported that a 5 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with a change in birthweight of 7.10 g (2.25, 12.00). Ebisu *et al*. (2016) observed a change birthweight of −4.15 g (−4.91, −3.40) for each 5 $\mu g/m^3$ increment in $PM_{2.5}$ exposure during the entire pregnancy among term-birth singleton infants in the US. Pedersen *et al*. (2013) reported a change in birthweight of –7 g (–17, 2) for term births, based on cohorts from 12 European countries. In a meta-analysis, the effect was estimated to be −7.9 g (−13.4, 2.5), and there was statistically significant heterogeneity among studies (Sun *et al*. 2016). These reports indicate a weak and unstable negative association between maternal exposure to $PM_{2.5}$ and birthweight change, which is consistent with our findings.

The associations between maternal exposure to $PM_{2.5}$ and birthweight (or LBW) in the US reportedly exhibit spatial variation. Parker and Woodruff (2008) examined the interaction

effects between regional indicators and $PM_{2.5}$, and reported that the $PM_{2.5}$-related reduction in birthweight was greater in the Northeast (birthweight change per 5 $\mu g/m^3$ increment in $PM_{2.5}$: -4.9 g; 95% CI: −13.3, 5.9 g) and industrial Midwest (−7.65 g; −21.7, 6.4 g). Hao *et al*. (2016) assessed the link between maternal exposure to $PM_{2.5}$ and the risk of a LBW in the contiguous US in 2002 using birth certificates and found higher odds ratios (OR) in the Mid-Atlantic, East North Central, and West North Central census divisions. The authors suggested that the spatial variations were due to (1) geographic variation in the sources of, and chemical species, in $PM_{2.5}$; (2) other environmental exposures that co-vary with $PM_{2.5}$ (*e.g.*, temperature); and (3) spatial differences in human behavior patterns (Hao *et al*. 2016). Our study confirms the spatial variation in the effects of $PM_{2.5}$ on birthweight, the pattern of which (higher effects in the Midwest and Northeast) was similar to those in the previous studies. However, we found an explainable pattern of effects that vary spatially. Because the state-level effect depends on characteristic susceptibilities of local populations, our spatial pattern can be explained by the geographical differences in demographic composition. Therefore, we can identify which individual-level characteristic plays a key role to explain the spatial variation through quantifying its contribution to the variance of state-level effects (Figure 5). Benefiting from the approach of human susceptibility distribution, this study quantifies part of the driving forces for the spatial heterogeneity in the $PM_{2.5}$-birthweight association for the first time, according to our best knowledge.

Additionally, it is worth to highlight that the spatial heterogeneity should not be over-interpreted, because of following weaknesses. First, the state-specific $PM_{2.5}$–birthweight associations depended on estimates of (1) individually-varied susceptibilities from the nation-scale data and (2) demographic structure of each state. The former estimates and their uncertainty were presumed to be unvaried between states, while accuracy of the latter was determined by how representative the valid samples are for the target population in each state. Although majority (> 70%) of the target individuals were involved into the valid records for all states (Figure 4), different fractions were excluded due to missing variables in birth certificates. Therefore, representativeness and uncertainty of the state-specific $PM_{2.5}$–birthweight associations might be different. Second, different magnitudes of state-specific associations should not be interpreted as $PM_{2.5}$-attributed risks, which depends on not only the

susceptibilities but also the polluted levels and health baselines. Without further exploration, we cannot distinguish whether the spatial heterogeneity in susceptibility considerably contribute to the geographic variation in health impacts from $PM_{2.5}$ exposure.

The individually-varied susceptibilities not only partially explained the spatial heterogeneity in the associations between $PM_{2.5}$ and birthweight, but also can implicate assessments of health impacts from $PM_{2.5}$ (Schwartz *et al.* 2011). When evaluating health risks of $PM_{2.5}$, most of existing studies (e.g., Zheng *et al.* 2017) were based on a uniform exposure-response function or functions by strata of a single effect-modifier (e.g., age). Therefore, the variability of health impacts of $PM_{2.5}$ might be dominated by different levels of pollution. However, in this study, we show that the variability of susceptibility is non-negligible and can be comparable with the variability of $PM_{2.5}$ concentration. Take our study as an example. The mean concentration of $PM_{2.5}$ in Texas was 17% higher than that in New Hampshire (11.8 $\mu g/m^3$ vs. 10.1 $\mu g/m^3$). In contrast, the mean susceptibility (i.e., birthweight reduction associated to per 5-$\mu g/m^3$ increment of $PM_{2.5}$) in the former was 85% (46%, 122%) lower than that in the latter (0.30 g [-0.41, 1.01] vs. 2.04 g [1.31, 2.76]). Because ignoring the differential susceptibilities can result in underestimating the variability in health impacts from $PM_{2.5}$, incorporating the approach of susceptibility distribution into the framework of risk assessment can not only improve understandings about health impacts from $PM_{2.5}$, but also support the risk-based health managements and interventions. For instance, given the considerable variability of susceptibility, a small fraction of vulnerable individuals may contribute to a large fraction of disease burden attributable to $PM_{2.5}$ (Schwartz *et al.* 2011). To protect them, the customized intervention such as tightened standards of ambient air quality or behavior shift toward low susceptibility is required.

Our study is limited in the following aspects. First, limited by data availability and the statistical approach, adjustment of confounders might be insufficient in our analyses. For instance, we ignored maternal body mass index, which is a key driver of birthweight but not reported by the database. Additionally, to avoid a large fraction of small-size subpopulations, we didn't categorize the effect-modifiers (e.g., maternal age, race and gestational length) into very specific strata, which might also lead to insufficient adjustment of confounders and thus bias the results (particularly the state-level results). Second, only 11 individual-level factors

were used to explain inter-individual differences in the effects of $PM_{2.5}$ on birthweight change. This may be insufficient to assess human susceptibility, which is complex. If significant modifiers were ignored, the variance of susceptibility distribution may have been underestimated (Figure 3). Third, susceptibility to ambient particles depends not only on the population characteristics but also the chemical species in the particles. Some components of particulate matters (*e.g.*, elemental carbon, polycyclic aromatic hydrocarbons, aluminum, nickel, and titanium in $PM_{2.5}$ and $PM_{2.5–10}$) are more strongly associated with a LBW (Dejmek 2000; Ebisu and Bell 2012; Ebisu *et al*. 2016). Because the sources of, and chemical species in, $PM_{2.5}$ varied geographically, the assumption that all particles are equally toxic could have introduced bias. For instance, the spatial difference in metals-related or biomass-burning-related sources (Thurston *et al.* 2011) may result in the variation of per-unit toxicity of $PM_{2.5}$ from north to south or from east to west. We plan to explore the joint effect of population characteristics and chemical species in a future study. Fourth, in this study, we interpret susceptibility as the absolute risk of per-unit increment in exposure, which might ignore the complexities underlying the concept of susceptibility. For instance, when quantifying susceptibility as the relative risk, it depends on both per-unit toxicity of $PM_{2.5}$ and baseline birthweight. Given that, it is complicated to understand the contribution to susceptibility from an effect-modifier that affects not only the $PM_{2.5}$-birthweight association but also baseline birthweight (e.g., gestational length, Web Figure 10). Fifth, we might ignore the complexities underlying the pairwise associations between gestational length, birthweight and $PM_{2.5}$. Because preterm birth has been linked to both LBW and $PM_{2.5}$ (Sun *et al.* 2015), gestational length can act as either a confounder or a mediator for the $PM_{2.5}$-birthweight association. To model susceptibility, this study incorporated the gestational length as a categorical variable, which is less accurate to characterize variability of fetal growth than the continuous format and thus impedes exploration of the pairwise associations. Sixth, we did not adjust for co-pollutants of $PM_{2.5}$, such as gaseous pollutants and noise, both of which are associated with birthweight and $PM_{2.5}$. Inclusion of the co-pollutants (*e.g.*, ozone) would have reduced the sample size; the large number of regression samples is the cornerstone of our analyses of susceptibility. Seventh, exposure misclassifications might arise from the usage of county-level averages of $PM_{2.5}$, as well as estimation of the pregnancy period. For instance, because the exposure time-window

was estimated using LMP and reported gestational length, it might be less accurate for assessment of exposure during the entire pregnancy or the third trimester (which is determined by both LMP and gestational length), compared with the first or second trimester (which is determined by LMP only). Therefore, the positive associations between $PM_{2.5}$ and birthweight change (Web Table) were inconclusive and should not be over-interpreted. Finally, of the two previous studies of the association between $PM_{2.5}$ and birthweight, one adjusted (Hao *et al*. 2016) for area-level socioeconomic status (*e.g.*, county-level poverty), while the other did not (Ebisu and Bell 2012). Because area-level socioeconomic statuses may also affect susceptibility to air pollution, inclusion of such variables would increase the complexity of the statistical models. Therefore, we ignored the area-level variables, which may also limit accuracy of our findings.

CONCLUSIONS

We present a state-of-the-art approach to identifying individual susceptibility to $PM_{2.5}$-related birthweight change in the contiguous US. Our results provide insight into not only the link between the risk of a reduced birthweight and maternal exposure to $PM_{2.5}$ but also the gradient variation in susceptibilities. These findings may be useful to the policymaker in planning interventions for subpopulations susceptible to ambient pollution.

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