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5 **Association between Birthweight and Ambient PM<sub>2.5</sub> in United States: Individually-**  
6 **varied Susceptibility and Spatial Heterogeneity**  
7

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1 **Abstract**

2 The association between maternal exposure to PM<sub>2.5</sub> and birthweight varies geographically,  
3 which may be caused by susceptibility. Whether this population-level association is a function  
4 of mixtures of individuals with different susceptibilities is unclear. We investigated the  
5 probability distribution of individuals with different susceptibilities to PM<sub>2.5</sub>-related  
6 birthweight change, and evaluated spatial variation of the effect across United States (US). We  
7 estimated the individual-level susceptibility using the effect of PM<sub>2.5</sub> among a homogenous  
8 subpopulation, which was defined by a specific combination of modifiers. According to  
9 frequencies for all combinations, we derived the probability distribution of differential  
10 susceptibilities across US and by states. From birth certificates across US (1999-2004), we  
11 analyzed a total of 18,317,707 samples of singletons. Of the samples, 54–55% were assigned  
12 valid exposures, and linked to PM<sub>2.5</sub>. The subpopulation-specific associations of PM<sub>2.5</sub> on  
13 birthweight change (*i.e.*, susceptibilities) ranged from negative to positive. For the first-  
14 trimester exposure, 61.4% of the associations were negative, and the mean was -1.01 g (95%  
15 confidence interval, CI: -1.63, -0.38) of birthweight change per 5 µg/m<sup>3</sup> increase of PM<sub>2.5</sub>. The  
16 state-level associations varied (from -2.04 g [-2.76, -1.31] in New Hampshire to -0.30 g [-1.01,  
17 0.41] in Texas) with demographic compositions in US. The between-state variation of maternal  
18 race and education level were the greatest contributors to the spatial heterogeneity. Our  
19 findings may be useful to the policymaker in planning interventions for subpopulations  
20 susceptible to ambient pollution.

21 **Keywords:** Fine particulate matter; PM<sub>2.5</sub>; birthweight; susceptibility; infant health

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121 **23 Introduction**

122  
123 24 Maternal exposure to ambient pollutants, including fine particulate matter with an aerodynamic  
124 25 diameter of less than 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ), is associated with decreased birthweight and the incidence  
125 26 of low birthweight (LBW) (Dadvand *et al.* 2013; Ebisu and Bell 2012; Ebisu *et al.* 2016; Hao  
126 27 *et al.* 2016; Parker and Woodruff 2008; Pedersen *et al.* 2013; Stieb *et al.* 2016), a risk factor  
127 28 for infant morbidity and mortality and development of diseases during adulthood (McCormick  
128 29 1985). However, these associations differ between studies (Dadvand *et al.* 2013; Sun *et al.*  
129 30 2016) and vary geographically (Ebisu *et al.* 2016; Hao *et al.* 2016; Parker and Woodruff 2008).  
130 31 Few studies have assessed the reasons underlying this heterogeneity. The effect on birthweight  
131 32 of a given ambient  $\text{PM}_{2.5}$  level varies among subpopulations; *e.g.*, different ethnicities (Ebisu  
132 33 and Bell 2012); this is termed differential susceptibility to  $\text{PM}_{2.5}$  (Bell *et al.* 2013; Sacks *et al.*  
133 34 2011). The fraction of susceptible individuals in the surveyed population varies among studies  
134 35 and geographically. Thus, a comprehensive evaluation of individual variations in susceptibility  
135 36 to  $\text{PM}_{2.5}$  is warranted.

136 37 The terms *susceptibility*, *vulnerability*, and *sensitivity* are used interchangeably to denote  
137 38 inter-individual variation in the risk of adverse health outcomes per unit increment in ambient  
138 39 exposure to pollutants (Bell *et al.* 2013). Regardless of the subtle distinctions among these  
139 40 terms, in this study we use *susceptibility* to represent the magnitude of toxicity of air pollution  
140 41 to an individual. Susceptibility is dependent on internal factors (*e.g.*, genetics and underlying  
141 42 disease[s]), external factors (*e.g.*, socioeconomic status), and exposure patterns (*e.g.*, travel).  
142 43 Epidemiological studies use the term ‘effect-modifier’ to denote these factors or their  
143 44 surrogates, and subject them to interaction analyses. However, previous studies explored single  
144 45 effect-modifiers separately. For example, the  $\text{PM}_{2.5}$ -LBW association is reportedly stronger  
145 46 among white mothers (Ebisu and Bell 2012). The simplicity of such studies may preclude  
146 47 evaluation of the different levels of susceptibility among the general population. Previous  
147 48 studies have reported three-way (Dubowsky *et al.* 2006) or higher-order interactions (Rosa *et*  
148 49 *al.* 2017) between the health effects of  $\text{PM}_{2.5}$  and individual characteristics, which indicates  
149 50 that multiple effect-modifiers might contribute to susceptibility both cumulatively and  
150 51 dependently. Additionally, few previous studies quantified the fraction of susceptible  
151 52 individuals among the general population, which is determined by not only the modifying  
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181 53 effects of individual characteristics but also their joint probability distribution among the target  
182 54 population.

184 55 To fully characterize susceptibility to PM<sub>2.5</sub>, we assume that the individual-specific health  
185 56 effect is determined by multiple effect-modifiers; thus, susceptibility may be quantified as a  
186 57 function of multiple variables at the level of the individual. Therefore, individuals with  
187 58 identical effect-modifiers have identical susceptibilities. In other words, the individual-specific  
188 59 effect (*i.e.*, susceptibility) can be estimated from a homogenous subpopulation. For the PM<sub>2.5</sub>-  
189 60 related birthweight change, we collected 11 infant and maternal variables as effect-modifiers  
190 61 or their surrogates to represent the gradient variation of individual-specific susceptibilities.  
191 62 These variables were selected according to previous findings and data availability, and are  
192 63 described in the following section. In this study, we quantify the individual-specific magnitudes  
193 64 of susceptibility as the birthweight change per unit increment of PM<sub>2.5</sub>, which are estimated in  
194 65 homogenous subgroups categorized by the 11 variables. By combining the different  
195 66 susceptibilities with the probabilities of the corresponding subgroups, we derived a new  
196 67 statistical measure, the ‘human susceptibility distribution’, which reflects both the magnitude  
197 68 and the prevalence of susceptibility in the general population.

199 69 Although several studies have linked nationwide data of birthweight or LBW to ambient  
200 70 particles (*e.g.*, PM<sub>2.5</sub> [Hao *et al.* 2016; Parker and Woodruff 2008], PM<sub>2.5</sub> [Ebisu and Bell 2012],  
201 71 PM<sub>2.5-10</sub> [Ebisu *et al.* 2016], and PM<sub>10</sub> [Parker and Woodruff 2008]) in the United States (US),  
202 72 none explored susceptibility to the effect of PM<sub>2.5</sub>. Using US birth certificates and the PM<sub>2.5</sub>  
203 73 concentrations monitored by national networks, we derived the human susceptibility  
204 74 distribution of the PM<sub>2.5</sub>-related change in birthweight. Furthermore, by considering  
205 75 geographic variation in the proportions of susceptible individuals in the US, we assessed the  
206 76 spatial variation of PM<sub>2.5</sub>-related birthweight change as a practical application of the human  
207 77 susceptibility distribution.

## 209 78 **METHODS**

### 210 79 **Study population**

211 80 Birth certificate data of the contiguous US from 1999 to 2004 were obtained from the National  
212 81 Center for Health Statistics, Centers for Disease Control and Prevention. This database was in  
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82 previous studies on the adverse effects of air pollutants on infants (*e.g.*, Hao *et al.* 2016). Many  
83 individual-level variables on both newborns and their mothers, such as county of residence,  
84 date of last menstrual period (LMP), and birthweight, were available during 1999–2004.  
85 Because many population characteristics could affect the susceptibility to PM<sub>2.5</sub>-related  
86 birthweight change, we targeted the 11 individual characteristics (Table 1) used as the  
87 modeling covariates in previous studies (Ebisu and Bell 2012; Ebisu *et al.* 2016).

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

100 Table 1. Characteristics of the Study Population.

Characteristic	Singleton births*	Valid records#	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%)

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

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

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

101 \* The target population.

102 # The samples used to calculate prevalence of susceptible individuals.

103 † The samples used to derive individual-level susceptibility.

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

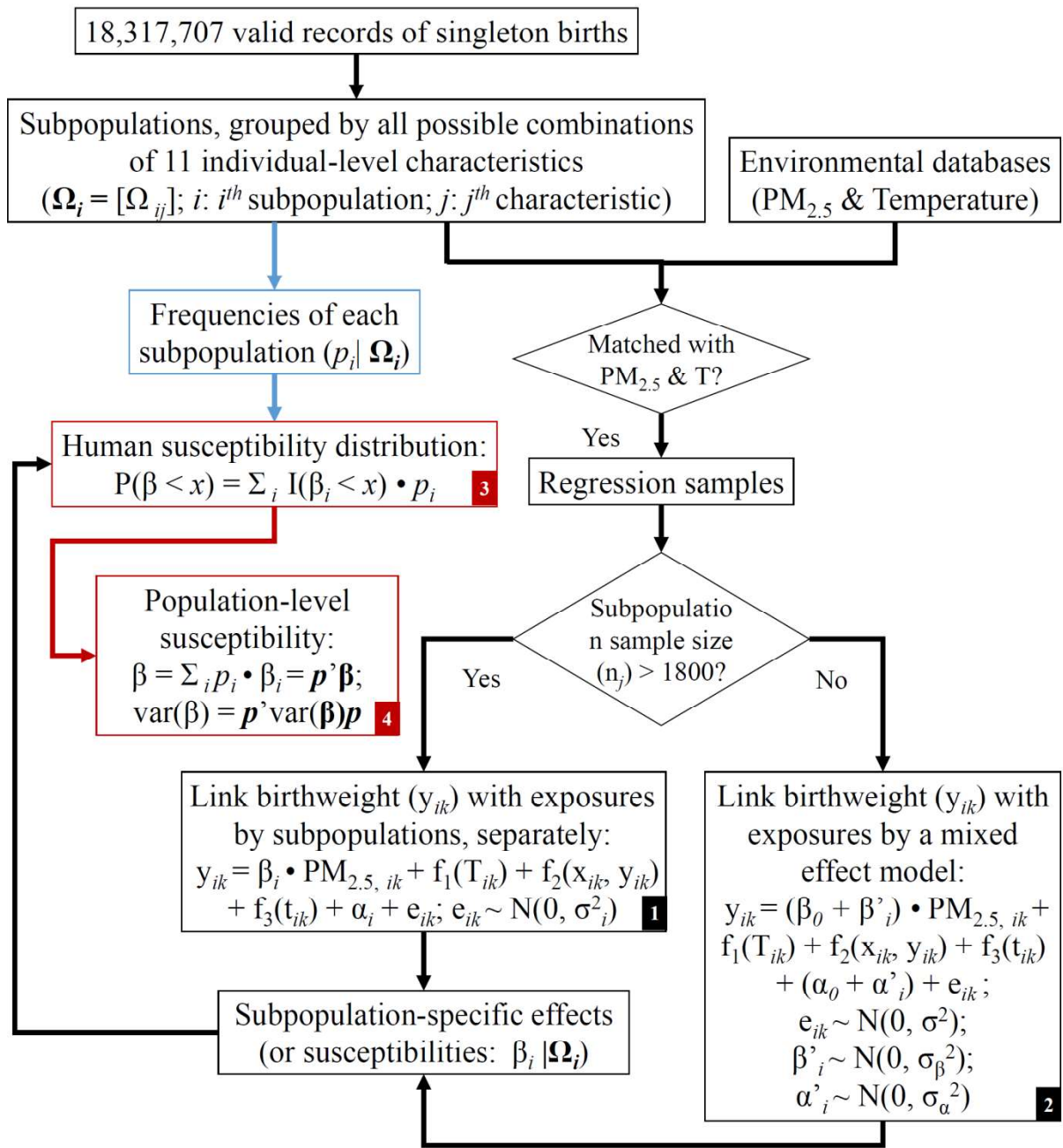
### 107 **Exposure assessment**

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

### 119 **Statistical analysis**

120 The statistical analysis procedure is shown in Figure 1. Briefly, among all birth records, those  
 121 assigned with environmental exposures (PM<sub>2.5</sub> and temperature) were used as regression  
 122 samples to link birthweight to maternal exposure to PM<sub>2.5</sub>. We used a batch of separate  
 123 regressions to derive subpopulation-specific susceptibilities. We also used all valid records to

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



126  
127 Figure 1. Statistical Analysis Procedure. Numbers (1–4) denote the equation indices. Black  
128 boxes show the derivation of subpopulation-specific susceptibilities; the blue box shows  
129 calculation of the frequency of each subpopulation; red boxes show the development and  
130 application of the susceptibility distribution.

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

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133 them, 8,632 were present in the population according to valid records of singleton births. Only  
134 a portion of the valid birth certificates (those used as regression samples) could be  
135 simultaneously assigned levels of exposure to both PM<sub>2.5</sub> and temperature, due to the  
136 incomplete spatiotemporal coverage of the monitoring networks. The sample sizes are  
137 summarized in Table 1.

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

153 Next, we approximated the probability that an individual belonged to a specific  
154 subpopulation ( $p_i | \Omega_i$ ) using the frequency of the subpopulation among all valid records of  
155 births. By considering the probability distribution of subpopulations ( $p_i | \Omega_i$ ) and the  
156 susceptibilities of these subpopulations to the PM<sub>2.5</sub>-related birthweight change ( $\beta_i | \Omega_i$ ), we  
157 assessed the human susceptibility distribution for maternal exposure during the entire  
158 pregnancy and each trimester according to Equation 3 (Figure 1).

159 Finally, we calculated the average susceptibility and its variance at the population level  
160 (Figure 1: Equation 4). We applied the approach to quantify population susceptibility to PM<sub>2.5</sub>-  
161 related birthweight change at the state level, and evaluated its spatial variation due to  
162 geographic differences in population composition.

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594 163 In sensitivity analyses, we derived the susceptibility distribution based on two different  
595 164 samples. First, through excluding variables on usage of alcohol and tobacco from the set of 11  
596 165 effect-modifiers, we included California births into our valid sample and regression samples  
597 166 and, re-estimated the susceptibility distribution based on 9 variables. Second, assuming the  
600 167 individual-level susceptibility also varies geographically, we incorporated an indicator for four  
601 168 US regions (Web Figure 1) as the additional effect-modifier, and re-estimated the susceptibility  
602 169 distribution based on 12 variables.

606 170 All statistical analyses were performed in R version 3.4.1 (R Core Team 2017). The mixed-  
607 171 effect models was conducted using the *lme4* package (Bates *et al.* 2014). The power curve was  
608 172 calculated using the *pwr* package (Champely 2017). The statistical significance level was set  
609 173 at 0.05.

## 614 174 **RESULTS**

### 616 175 **Descriptive statistics**

618 176 During the study period, there were 24,135,665 births in the contiguous U.S., and 23,354,466  
619 177 of them were singletons. After exclusions, the study dataset comprised 18,317,707 valid  
620 178 records of singleton births. Among them, 54–55% (about 10 million, Table 1) that were  
621 179 assigned valid environmental exposures (both PM<sub>2.5</sub> and temperature) during the whole  
622 180 pregnancy or one trimester were subjected to regression analysis of birthweight. The spatial  
623 181 distribution of the infants is shown in Web Figure 1, together with the PM<sub>2.5</sub>-monitoring  
624 182 locations. California was excluded from the main analysis, because maternal use of alcohol or  
625 183 tobacco was not reported there during the study period. The regression samples covered most  
626 184 other populous areas.

634 185 The infant and maternal characteristics for (1) all singleton births, (2) valid records after  
635 186 application of the exclusion criteria, and (3) regression samples are summarized in Table 1.  
636 187 The three types of samples were similar in most of the characteristics, which suggested that the  
637 188 exclusions did not considerably change the demographic composition of the study population.  
638 189 The regression samples had a slightly higher fraction of births with a maternal education level  
639 190 of > 12 years (51.5% vs. 47.7%), because these tended to be from urban or suburban areas. The  
640 191 summary statistics for the continuous variables (*i.e.*, birthweight, PM<sub>2.5</sub>, and temperature) are

presented in Table 2. The mean birthweight was 3.34 kg, and the mean PM<sub>2.5</sub> level was 13.1 µg/m<sup>3</sup>. 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 <sub>2.5</sub> µg/m <sup>3</sup>	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 <sub>2.5</sub> µg/m <sup>3</sup>	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 <sub>2.5</sub> µg/m <sup>3</sup>	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 <sub>2.5</sub> µg/m <sup>3</sup>	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

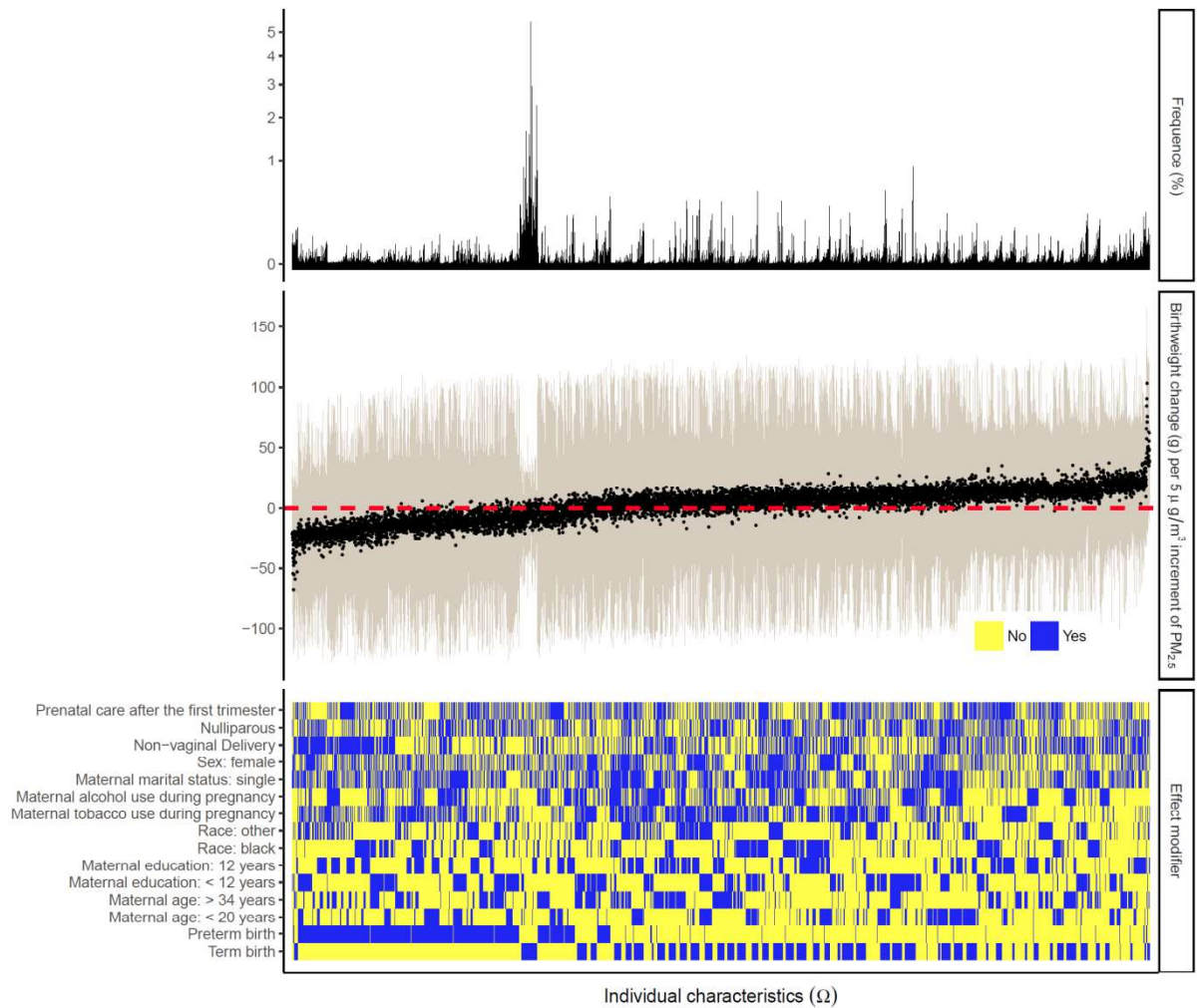
### Individual-specific susceptibility

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<sub>2.5</sub> 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 µg/m<sup>3</sup> increment of PM<sub>2.5</sub> 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

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206 PM<sub>2.5</sub> level was significantly associated with decreased birthweight during the entire pregnancy  
207 and the first two trimesters. The association was significantly stronger in the ID 2  
208 subpopulation than the ID1 subpopulation.

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211 Figure 2. Estimated Effects (middle panel) of Maternal Exposure to PM<sub>2.5</sub> during the First  
212 Trimester on Birthweight in all Subpopulations, Classified According to Combinations of  
213 Individual-level Effect-modifiers (bottom panel), with the Probability Distribution (top panel)  
214 of those Subpopulations in the Contiguous US. The Order of Combinations is Determined  
215 Using a Clustering Method, Which Tends to Put Individuals with Similar Characteristics and  
216 Susceptibility Together.

217 The estimated effects from the subpopulation-specific regressions, together with their  
218 frequencies, are shown in Figure 2 (first trimester) and Web Figures 3–5 (second trimester,  
219 third trimester, and entire pregnancy). The associations between maternal exposure to PM<sub>2.5</sub>

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220 and birthweight change varied markedly according to the combinations of individual  
221 characteristics, and the associations were negative for most of the populous subgroups  
222 (frequency > 1%). Because the individuals within a subpopulation are homogenous, the  
223 variable effects reflect the gradient variation of individual susceptibilities to PM<sub>2.5</sub> among the  
224 general population.

225 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:
4	Male	20-34 years	> 12 years	Nulliparous	Vaginal	Married; Gestational length: Term;
5	Male	20-34 years	12 years	Parous	Vaginal	Prenatal care: From first trimester;
6	Female	20-34 years	12 years	Parous	Vaginal	Maternal tobacco use during pregnancy: No;
7	Male	> 35 years	> 12 years	Parous	Vaginal	Maternal alcohol use during pregnancy: No.
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	

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228 Table 4 Birthweight-PM<sub>2.5</sub> Associations for the Largest 10 Subpopulations. Significant effects  
229 are shown in bold in the bottom table ( $P < 0.05$ ).

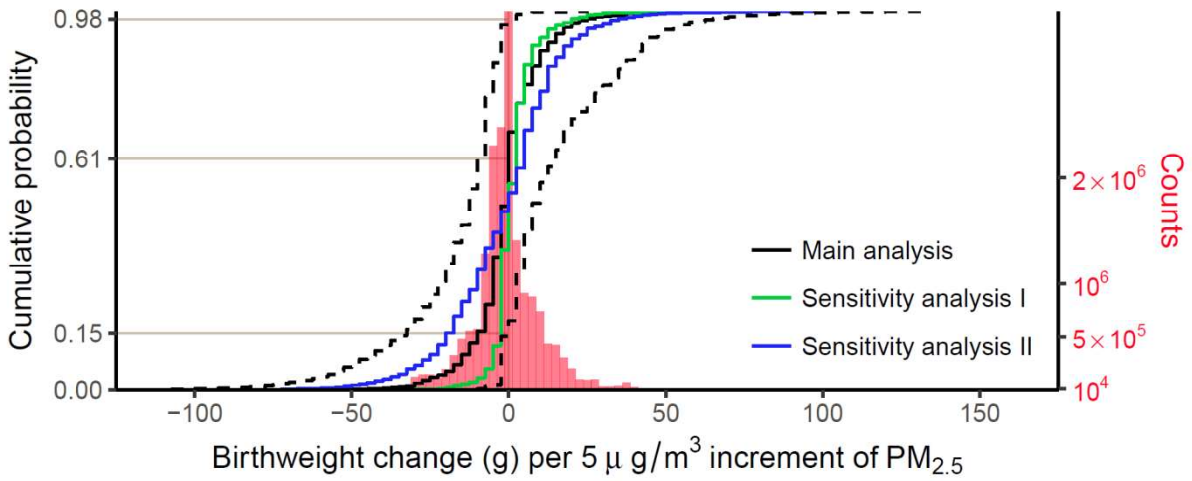
ID	Counts of valid records (percentage)	Birthweight change (g) per 5 $\mu\text{g}/\text{m}^3$ increment of PM <sub>2.5</sub> (95% CI)			
		Entire pregnancy	first trimester	second trimester	third trimester
1	996,906 (5.4%)	1.38 (-2.40, 5.15)	-0.61 (-3.08, 1.86)	-1.76 (-4.15, 0.63)	1.51 (-0.93, 3.96)
2	971,410 (5.3%)	<b>-4.24</b> <b>(-7.95, -0.54)</b>	<b>-4.34</b> <b>(-6.76, -1.92)</b>	<b>-3.63</b> <b>(-5.98, -1.28)</b>	0.38 (-2.02, 2.77)
3	540,797 (3.0%)	-1.97 (-6.76, 2.81)	<b>-4.57</b> <b>(-7.72, -1.42)</b>	-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%)	<b>-9.51</b> <b>(-16.44, -2.57)</b>	<b>-7.42</b> <b>(-12.04, -2.80)</b>	<b>-6.73</b> <b>(-11.21, -2.25)</b>	-1.44 (-5.99, 3.12)
8	296,404 (1.6%)	<b>-9.47</b> <b>(-16.22, -2.72)</b>	<b>-7.92</b> <b>(-12.40, -3.44)</b>	<b>-7.51</b> <b>(-11.86, -3.15)</b>	-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%)	<b>-9.72</b> <b>(-17.61, -1.84)</b>	0.53 (-4.79, 5.84)	<b>-5.68</b> <b>(-10.91, -0.46)</b>	<b>-8.49</b> <b>(-13.78, -3.21)</b>

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231 **Susceptibility probability distribution**

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234 Figure 3. Probability Distribution for Susceptibility to Birthweight Change Related to Maternal  
235 Exposure to PM<sub>2.5</sub> during the First Trimester for Singleton Births in the Contiguous US. The  
236 Green and Blue Solid Lines Present the Estimated Cumulative Probability Functions in  
237 Sensitive Analyses. Sensitivity Analysis I: Inclusion of California Births and Exclusion of  
238 Alcohol/Tobacco Use in the Set of Effect-modifiers; Sensitivity Analysis II: Inclusion of the  
239 Regional Indicator in the Set of Effect-modifiers.

240 By combining the susceptibilities to PM<sub>2.5</sub> with the probability distribution of individuals, we  
241 derived the susceptibility distribution of the PM<sub>2.5</sub>-related birthweight changes for singleton  
242 births in the contiguous US (Figure 3 [first trimester] and Web Figures 6–8 [second trimester,  
243 third trimester, and entire pregnancy]). The susceptibility distribution was centered close to  
244 zero. The median effects were 0.54, -0.89, -1.76, and 1.51 g changes in birthweight per 5 μg/m<sup>3</sup>  
245 increment of PM<sub>2.5</sub> during the entire pregnancy and the first, second, and third trimesters,  
246 respectively (Table 5). There were more statistically negative effects than statistically positive  
247 ones (Table 5). Particularly, the effects were negative for more than 50% of the births for  
248 exposure for maternal exposure during the first (61.4%) and second (65.4%) trimesters. The  
249 distributional susceptibilities suggested that each increment in maternal exposure to PM<sub>2.5</sub>,  
250 especially during the first two trimesters, was likely to lead to a reduced birthweight, which is  
251 consistent with previous reports.

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253 Table 5. Summary Statistics for the Distributions of the Estimated Effects of PM<sub>2.5</sub> on  
254 Birthweight by Subpopulation in the Contiguous US.

Statistics	Effect: birthweight change (g) per 5 µg/m <sup>3</sup> increment of PM <sub>2.5</sub>			
	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%

255 **Population-level susceptibility: the weighted average**

256 We quantified the average effect of PM<sub>2.5</sub> on birthweight within a target population (defined as  
257 population-level susceptibility) as the probability-weighted mean of the individual  
258 susceptibilities. The target populations were all singleton births in the contiguous US and  
259 subsets thereof (*e.g.*, all female births or births in a specific state). Web Table shows the  
260 population-level susceptibilities for our study population and of subsets defined by single  
261 individual-level factors. More description in the Web Appendix.

262 **Spatial variation of state-level susceptibility**

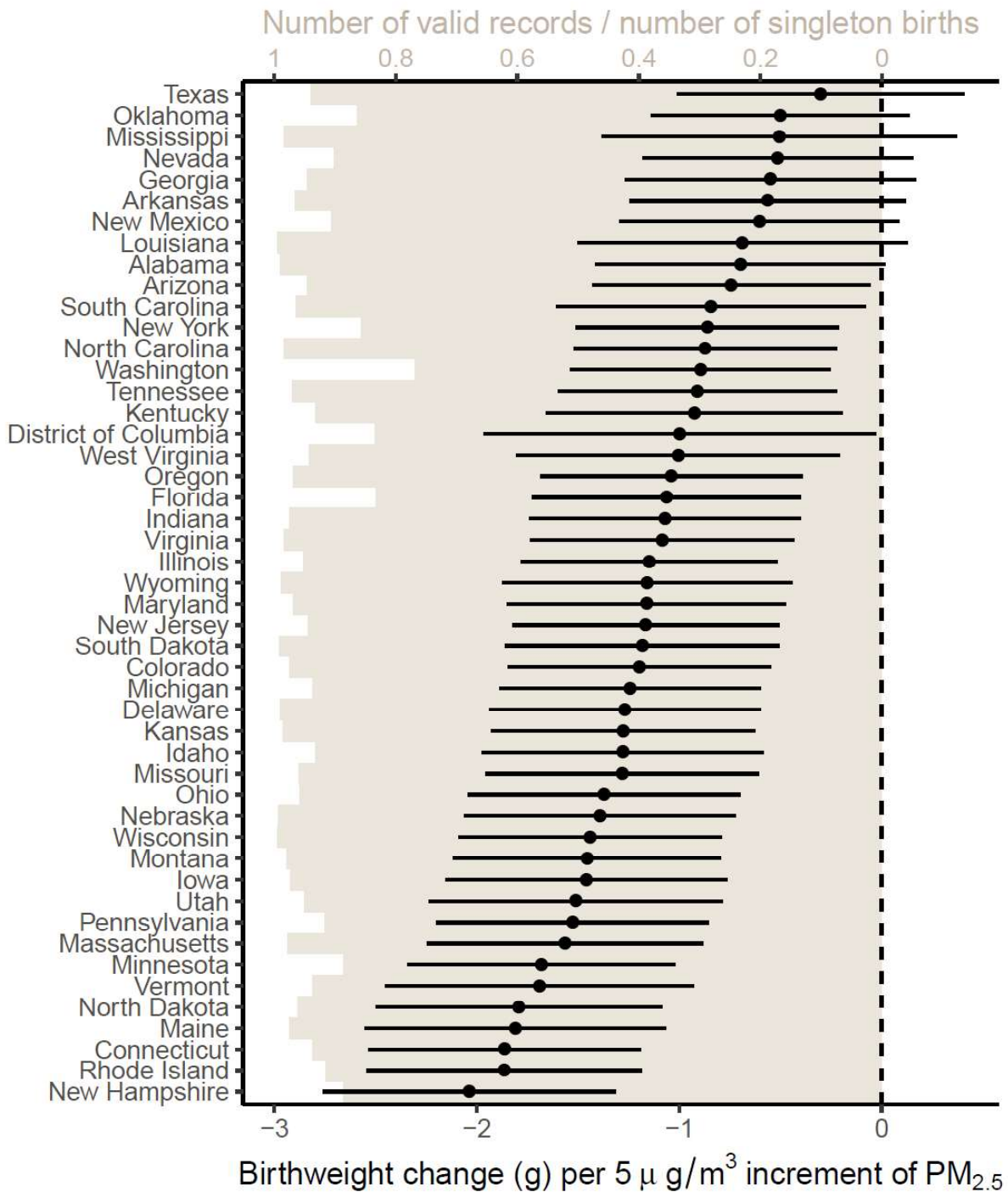


Figure 4. Spatial Variation of Susceptibility to Birthweight Change Related to Maternal Exposure to  $\text{PM}_{2.5}$  during the First Trimester. The gray bar presents a ratio of the number of valid records against the number of singleton births (i.e., target population) in each county. The level of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

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

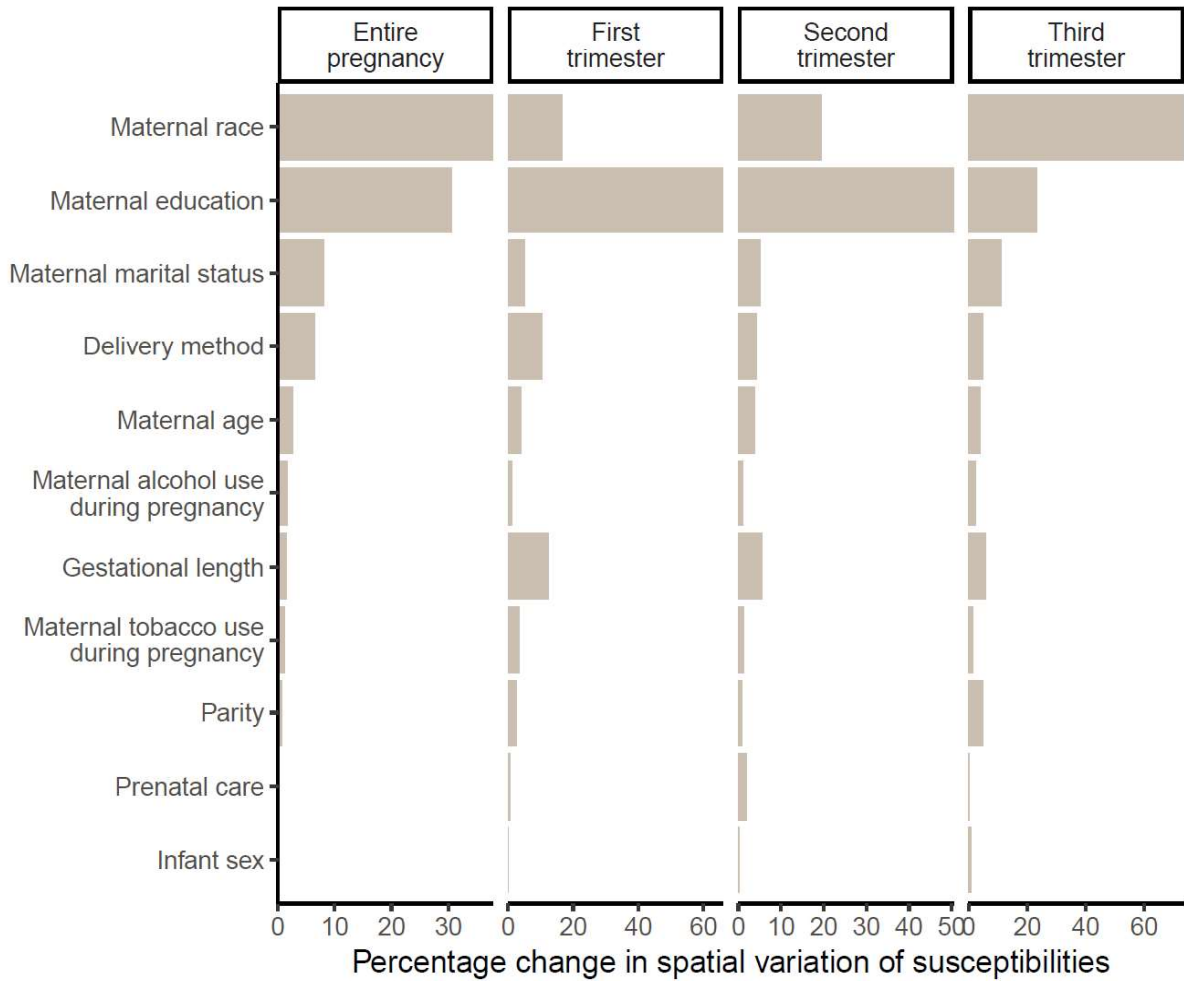


Figure 5. Contributions of the 11 Population Characteristics to the Spatial Variance of State-level Susceptibility.

### 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-dependent 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-dependent variables. For instance, in the second sensitivity analysis, after incorporating the geographic indicator, the susceptibility distribution becomes dispersed,

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1243 298 which suggests that some spatially-varying factors unmeasured in this study may also  
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1245 299 contribute to the variation of susceptibility. Such factors can belong to population  
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1247 300 characteristics like the 11 effect-modifiers or to other aspects, such as chemical components of  
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1249 301 PM<sub>2.5</sub>. Because this study is focused on the explainable susceptibility that depends on  
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1251 302 individual-level variables rather than other aspects, the results are interpreted based on the  
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1253 303 model without the geographic indicator.

## 1254 304 **DISCUSSION**

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1256 305 Unlike traditional studies, which associated maternal ambient exposure to birthweight after  
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1258 306 adjusting for several covariates, we regressed birthweight with PM<sub>2.5</sub> independently within  
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1260 307 different subpopulations. Using birth certificates, we estimated individual susceptibility to  
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1262 308 PM<sub>2.5</sub>-related birthweight change according to type of birth in the contiguous US, and  
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1264 309 determined for the first time the susceptibility distribution in the general population.

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1266 310 The effect of maternal exposure to PM<sub>2.5</sub> on birthweight varied among individuals from  
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1268 311 negative to positive, and was not statistically significant for most of the study population (*i.e.*,  
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1270 312 82.20% 83.00% 85.20% 89.60% for exposure during the entire pregnancy and the first,  
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1272 313 second, and third trimesters, respectively). However, the effect had a higher probability of  
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1274 314 being significantly negative (Table 5). Such variation of the effect is consistent with previous  
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1276 315 reports. Parker and Woodruff (2008) linked birthweight to 9-month exposure to PM<sub>2.5</sub> among  
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1278 316 singleton births delivered at 40 weeks of gestation in the US, and reported that a 5 µg/m<sup>3</sup>  
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1280 317 increment in PM<sub>2.5</sub> was associated with a change in birthweight of 7.10 g (2.25, 12.00). Ebisu  
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1282 318 *et al.* (2016) observed a change birthweight of -4.15 g (-4.91, -3.40) for each 5 µg/m<sup>3</sup>  
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1284 319 increment in PM<sub>2.5</sub> exposure during the entire pregnancy among term-birth singleton infants in  
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1286 320 the US. Pedersen *et al.* (2013) reported a change in birthweight of -7 g (-17, 2) for term births,  
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1288 321 based on cohorts from 12 European countries. In a meta-analysis, the effect was estimated to  
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1290 322 be -7.9 g (-13.4, 2.5), and there was statistically significant heterogeneity among studies (Sun  
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1292 323 *et al.* 2016). These reports indicate a weak and unstable negative association between maternal  
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1294 324 exposure to PM<sub>2.5</sub> and birthweight change, which is consistent with our findings.

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1296 325 The associations between maternal exposure to PM<sub>2.5</sub> and birthweight (or LBW) in the US  
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1298 326 reportedly exhibit spatial variation. Parker and Woodruff (2008) examined the interaction

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1302 327 effects between regional indicators and PM<sub>2.5</sub>, and reported that the PM<sub>2.5</sub>-related reduction in  
1303 328 birthweight was greater in the Northeast (birthweight change per 5 µg/m<sup>3</sup> increment in PM<sub>2.5</sub>:  
1305 329 -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)  
1306 330 assessed the link between maternal exposure to PM<sub>2.5</sub> and the risk of a LBW in the contiguous  
1308 331 US in 2002 using birth certificates and found higher odds ratios (OR) in the Mid-Atlantic, East  
1310 332 North Central, and West North Central census divisions. The authors suggested that the spatial  
1312 333 variations were due to (1) geographic variation in the sources of, and chemical species, in PM<sub>2.5</sub>;  
1314 334 (2) other environmental exposures that co-vary with PM<sub>2.5</sub> (*e.g.*, temperature); and (3) spatial  
1316 335 differences in human behavior patterns (Hao *et al.* 2016). Our study confirms the spatial  
1317 336 variation in the effects of PM<sub>2.5</sub> on birthweight, the pattern of which (higher effects in the  
1318 337 Midwest and Northeast) was similar to those in the previous studies. However, we found an  
1319 338 explainable pattern of effects that vary spatially. Because the state-level effect depends on  
1320 339 characteristic susceptibilities of local populations, our spatial pattern can be explained by the  
1321 340 geographical differences in demographic composition. Therefore, we can identify which  
1322 341 individual-level characteristic plays a key role to explain the spatial variation through  
1323 342 quantifying its contribution to the variance of state-level effects (Figure 5). Benefiting from the  
1324 343 approach of human susceptibility distribution, this study quantifies part of the driving forces  
1325 344 for the spatial heterogeneity in the PM<sub>2.5</sub>-birthweight association for the first time, according  
1326 345 to our best knowledge.

1336 346 Additionally, it is worth to highlight that the spatial heterogeneity should not be over-  
1337 347 interpreted, because of following weaknesses. First, the state-specific PM<sub>2.5</sub>-birthweight  
1338 348 associations depended on estimates of (1) individually-varied susceptibilities from the nation-  
1339 349 scale data and (2) demographic structure of each state. The former estimates and their  
1340 350 uncertainty were presumed to be unvaried between states, while accuracy of the latter was  
1341 351 determined by how representative the valid samples are for the target population in each state.  
1342 352 Although majority (> 70%) of the target individuals were involved into the valid records for  
1343 353 all states (Figure 4), different fractions were excluded due to missing variables in birth  
1344 354 certificates. Therefore, representativeness and uncertainty of the state-specific PM<sub>2.5</sub>-  
1345 355 birthweight associations might be different. Second, different magnitudes of state-specific  
1346 356 associations should not be interpreted as PM<sub>2.5</sub>-attributed risks, which depends on not only the  
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1361 357 susceptibilities but also the polluted levels and health baselines. Without further exploration,  
1362 358 we cannot distinguish whether the spatial heterogeneity in susceptibility considerably  
1363 359 contribute to the geographic variation in health impacts from PM<sub>2.5</sub> exposure.

1366 360 The individually-varied susceptibilities not only partially explained the spatial  
1367 361 heterogeneity in the associations between PM<sub>2.5</sub> and birthweight, but also can implicate  
1368 362 assessments of health impacts from PM<sub>2.5</sub> (Schwartz *et al.* 2011). When evaluating health risks  
1370 363 of PM<sub>2.5</sub>, most of existing studies (e.g., Zheng *et al.* 2017) were based on a uniform exposure-  
1371 364 response function or functions by strata of a single effect-modifier (e.g., age). Therefore, the  
1372 365 variability of health impacts of PM<sub>2.5</sub> might be dominated by different levels of pollution.  
1373 366 However, in this study, we show that the variability of susceptibility is non-negligible and can  
1374 367 be comparable with the variability of PM<sub>2.5</sub> concentration. Take our study as an example. The  
1375 368 mean concentration of PM<sub>2.5</sub> in Texas was 17% higher than that in New Hampshire (11.8 µg/m<sup>3</sup>  
1376 369 vs. 10.1 µg/m<sup>3</sup>). In contrast, the mean susceptibility (i.e., birthweight reduction associated to  
1377 370 per 5-µg/m<sup>3</sup> increment of PM<sub>2.5</sub>) in the former was 85% (46%, 122%) lower than that in the  
1378 371 latter (0.30 g [-0.41, 1.01] vs. 2.04 g [1.31, 2.76]). Because ignoring the differential  
1379 372 susceptibilities can result in underestimating the variability in health impacts from PM<sub>2.5</sub>,  
1380 373 incorporating the approach of susceptibility distribution into the framework of risk assessment  
1381 374 can not only improve understandings about health impacts from PM<sub>2.5</sub>, but also support the  
1382 375 risk-based health managements and interventions. For instance, given the considerable  
1383 376 variability of susceptibility, a small fraction of vulnerable individuals may contribute to a large  
1384 377 fraction of disease burden attributable to PM<sub>2.5</sub> (Schwartz *et al.* 2011). To protect them, the  
1385 378 customized intervention such as tightened standards of ambient air quality or behavior shift  
1386 379 toward low susceptibility is required.

1400 380 Our study is limited in the following aspects. First, limited by data availability and the  
1401 381 statistical approach, adjustment of confounders might be insufficient in our analyses. For  
1402 382 instance, we ignored maternal body mass index, which is a key driver of birthweight but not  
1403 383 reported by the database. Additionally, to avoid a large fraction of small-size subpopulations,  
1404 384 we didn't categorize the effect-modifiers (e.g., maternal age, race and gestational length) into  
1405 385 very specific strata, which might also lead to insufficient adjustment of confounders and thus  
1406 386 bias the results (particularly the state-level results). Second, only 11 individual-level factors  
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387 were used to explain inter-individual differences in the effects of PM<sub>2.5</sub> on birthweight change.  
388 This may be insufficient to assess human susceptibility, which is complex. If significant  
389 modifiers were ignored, the variance of susceptibility distribution may have been  
390 underestimated (Figure 3). Third, susceptibility to ambient particles depends not only on the  
391 population characteristics but also the chemical species in the particles. Some components of  
392 particulate matters (*e.g.*, elemental carbon, polycyclic aromatic hydrocarbons, aluminum,  
393 nickel, and titanium in PM<sub>2.5</sub> and PM<sub>2.5-10</sub>) are more strongly associated with a LBW (Dejmek  
394 2000; Ebisu and Bell 2012; Ebisu *et al.* 2016). Because the sources of, and chemical species  
395 in, PM<sub>2.5</sub> varied geographically, the assumption that all particles are equally toxic could have  
396 introduced bias. For instance, the spatial difference in metals-related or biomass-burning-  
397 related sources (Thurston *et al.* 2011) may result in the variation of per-unit toxicity of PM<sub>2.5</sub>  
398 from north to south or from east to west. We plan to explore the joint effect of population  
399 characteristics and chemical species in a future study. Fourth, in this study, we interpret  
400 susceptibility as the absolute risk of per-unit increment in exposure, which might ignore the  
401 complexities underlying the concept of susceptibility. For instance, when quantifying  
402 susceptibility as the relative risk, it depends on both per-unit toxicity of PM<sub>2.5</sub> and baseline  
403 birthweight. Given that, it is complicated to understand the contribution to susceptibility from  
404 an effect-modifier that affects not only the PM<sub>2.5</sub>-birthweight association but also baseline  
405 birthweight (*e.g.*, gestational length, Web Figure 10). Fifth, we might ignore the complexities  
406 underlying the pairwise associations between gestational length, birthweight and PM<sub>2.5</sub>.  
407 Because preterm birth has been linked to both LBW and PM<sub>2.5</sub> (Sun *et al.* 2015), gestational  
408 length can act as either a confounder or a mediator for the PM<sub>2.5</sub>-birthweight association. To  
409 model susceptibility, this study incorporated the gestational length as a categorical variable,  
410 which is less accurate to characterize variability of fetal growth than the continuous format and  
411 thus impedes exploration of the pairwise associations. Sixth, we did not adjust for co-pollutants  
412 of PM<sub>2.5</sub>, such as gaseous pollutants and noise, both of which are associated with birthweight  
413 and PM<sub>2.5</sub>. Inclusion of the co-pollutants (*e.g.*, ozone) would have reduced the sample size; the  
414 large number of regression samples is the cornerstone of our analyses of susceptibility. Seventh,  
415 exposure misclassifications might arise from the usage of county-level averages of PM<sub>2.5</sub>, as  
416 well as estimation of the pregnancy period. For instance, because the exposure time-window

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1479 417 was estimated using LMP and reported gestational length, it might be less accurate for  
1480 418 assessment of exposure during the entire pregnancy or the third trimester (which is determined  
1481 419 by both LMP and gestational length), compared with the first or second trimester (which is  
1482 420 determined by LMP only). Therefore, the positive associations between PM<sub>2.5</sub> and birthweight  
1483 421 change (Web Table) were inconclusive and should not be over-interpreted. Finally, of the two  
1484 422 previous studies of the association between PM<sub>2.5</sub> and birthweight, one adjusted (Hao *et al.*  
1485 423 2016) for area-level socioeconomic status (*e.g.*, county-level poverty), while the other did not  
1486 424 (Ebisu and Bell 2012). Because area-level socioeconomic statuses may also affect  
1487 425 susceptibility to air pollution, inclusion of such variables would increase the complexity of the  
1488 426 statistical models. Therefore, we ignored the area-level variables, which may also limit  
1489 427 accuracy of our findings.

## 1498 428 **CONCLUSIONS**

1499 429 We present a state-of-the-art approach to identifying individual susceptibility to PM<sub>2.5</sub>-related  
1500 430 birthweight change in the contiguous US. Our results provide insight into not only the link  
1501 431 between the risk of a reduced birthweight and maternal exposure to PM<sub>2.5</sub> but also the gradient  
1502 432 variation in susceptibilities. These findings may be useful to the policymaker in planning  
1503 433 interventions for subpopulations susceptible to ambient pollution.

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