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Effects of Prenatal Exposure to $PM_{2.5}$ Chemical Components on Adverse Birth Outcomes and Under-5 Mortality in South Korea

Garam Byun,[a,b] Yongsoo Choi,[a,b] Jong-Tae Lee,[b,c,d] and Michelle L. Bell[a,d]

Background: Exposure to fine particulate matter ($PM_{2.5}$) during pregnancy has been associated with adverse birth outcomes. However, limited evidence exists on the effects of specific $PM_{2.5}$ components. We investigated the association of prenatal exposure to $PM_{2.5}$ and its components with birth outcomes and mortality at age <5 years in four metropolitan cities in South Korea.

Methods: We obtained data from Statistic Korea linking birth records for 2013–2015 to death records under age 5 years. Data for $PM_{2.5}$ and 10 of its components were collected from four monitoring stations. We calculated exposures during pregnancy and each trimester for a total of 324,566 births. We used logistic regression to estimate the associations between exposure and risk of preterm birth (PTB) (<37 weeks), low birth weight (<2.5 kg), small for gestational age (birth weight <10th percentile for the same gestational age), and under-5 mortality.

Results: An interquartile range (8.7 μg/m³) increase in exposure to $PM_{2.5}$ during the entire pregnancy was associated with increased odds of PTB (odds ratio [OR] = 1.17; 95% confidence interval [CI] = 1.11, 1.23). We observed no association with low birth weight, small for gestational age, or under-5 mortality for the entire pregnancy exposure. Elemental carbon and secondary inorganic aerosols showed higher effect estimates for PTB than did other components.

Conclusions: In urban populations of South Korea, exposure to $PM_{2.5}$ during pregnancy was associated with an increased risk of PTB. Different components showed varying associations with adverse birth outcomes.

Keywords: Birth cohort; Child mortality; Low birth weight; Maternal exposure; Particulate matter; Pregnancy outcome; Premature birth; Small for gestational age

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From the [a]School of the Environment, Yale University, New Haven, CT; [b]Research and Management Center for Health Risk of Particulate Matter, Seoul, Republic of Korea; [c]Interdisciplinary Program in Precision Public Health, Department of Public Health Sciences, Graduate School of Korea University, Seoul, Republic of Korea; and [d]School of Health Policy and Management, College of Health Sciences, Korea University, Seoul, Republic of Korea

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The authors report no conflicts of interest.

The birth–death linked dataset is accessible through Microdata Integrated Service of Statistics Korea. The exposure dataset cannot be shared by the authors due to restrictions on distribution. The computing code used to generate the results may be requested from the corresponding author.

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Correspondence: Jong-Tae Lee, Department of Public Health Sciences, Korea University, 145, Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea. E-mail: jtlee@korea.ac.kr.

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Adverse birth outcomes, such as low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA), can lead to both immediate and long-term health problems for infants. These issues range from increased susceptibility to infections and developmental delays to higher risk for chronic diseases, including heart disease and diabetes later in life, and even mortality.[1–3] Such adverse birth outcomes often stem from intrauterine growth restriction and might indicate maternal health problems, including hypertension, kidney disease, malnutrition, and substance misuse.[4]

According to the World Health Organization (WHO), approximately 13.4 million babies were born preterm in 2020, accounting for about 1 in 10 of all births worldwide.[5] LBW affects an estimated 20 million newborns each year, representing approximately 16% of all births.[6] SGA is defined as a birth weight below the 10th percentile for gestational age, suggesting that approximately 10% of all newborns are expected to be classified as SGA. However, this proportion can vary with the choice of reference population. Using the 1991 US national reference population, Lee et al.[7] estimated that 27% of live births in low-income and middle-income countries in 2010 were classified as SGA. Under-5 mortality rates, although declining, remain a substantial concern; in 2022, 4.9 million children died before reaching their fifth birthday.[8] South Korea has made substantial advancements in healthcare, reflected in its notably low under-5 mortality rate of around 3 per 1,000 live births in 2022.[8] However, the incidence rates of LBW and PTB, which were about 7.2%

and 9.2%, respectively, in 2021, have shown an upward trend in recent years.[9]

The occurrence of adverse birth outcomes and child mortality is influenced by a combination of genetic, social, and environmental factors. Among these, exposure to fine particulate matter (particulate matter with an aerodynamic diameter ≤2.5 µm, $PM_{2.5}$) during pregnancy has emerged as an important environmental risk factor. Inhaled $PM_{2.5}$ has the potential to induce systemic inflammation and oxidative stress, which may adversely affect fetal development.[10] Previous systematic reviews and meta-analyses showed that exposure to $PM_{2.5}$ is associated with increased risk of LBW, PTB, SGA, stillbirth, and infant and child mortality.[11,12]

$PM_{2.5}$ is a complex mixture of various chemical constituents, including but not limited to organic compounds, metals, and inorganic ions. While the specific chemical components of these particles are thought to play a critical role,[13,14] the exact component(s) that are most harmful are not fully understood. Knowledge of which characteristics of $PM_{2.5}$ contribute to the highest health burden could inform public health strategies, as the composition of $PM_{2.5}$ is closely linked to its sources.[15] Despite the importance of understanding which types of particles are most harmful, previous research offers limited and inconclusive evidence regarding the impacts of specific $PM_{2.5}$ components on adverse birth outcomes and under-5 mortality.[16,17]

The body of evidence is particularly scant in the Asian context, and to the best of our knowledge, no studies have specifically examined the chemical components of $PM_{2.5}$ in relation to adverse birth outcomes or child mortality in South Korea. Therefore, this study aimed to investigate the association of prenatal exposure to $PM_{2.5}$ and its components with birth outcomes, including PTB, LBW, SGA, and under-5 mortality in South Korea.

METHODS

Study Population and Outcome Assessment

We obtained birth certificate data from 2013 to 2015 merged with death records for persons under the age of five from Statistic Korea. Specifically, infants born in the year 2013 were linked with death certificates from the period 2013–2018, 2014–2019 for those born in 2014, and 2015–2020 for those born in 2015. This birth–death-linked dataset included information on the date of birth, residential area at birth at the district level (referred to as si-gun-gu in South Korea, which is roughly analogous to a borough in the US); gestational week; infant's sex and birth weight; birth order; plurality; maternal marital status; and both maternal and paternal ages, education levels, occupations, and nationality. For those who died before 5 years, the dataset also contained information on the date, district, and cause of death, as well as the age at which the death occurred.

The study population was restricted to infants born in four metropolitan cities in South Korea (Seoul, Gwangju, Daejeon, and Ulsan) owing to the availability of $PM_{2.5}$ component data exclusively for these locations. The average land area of the four cities is approximately 676 km², and they

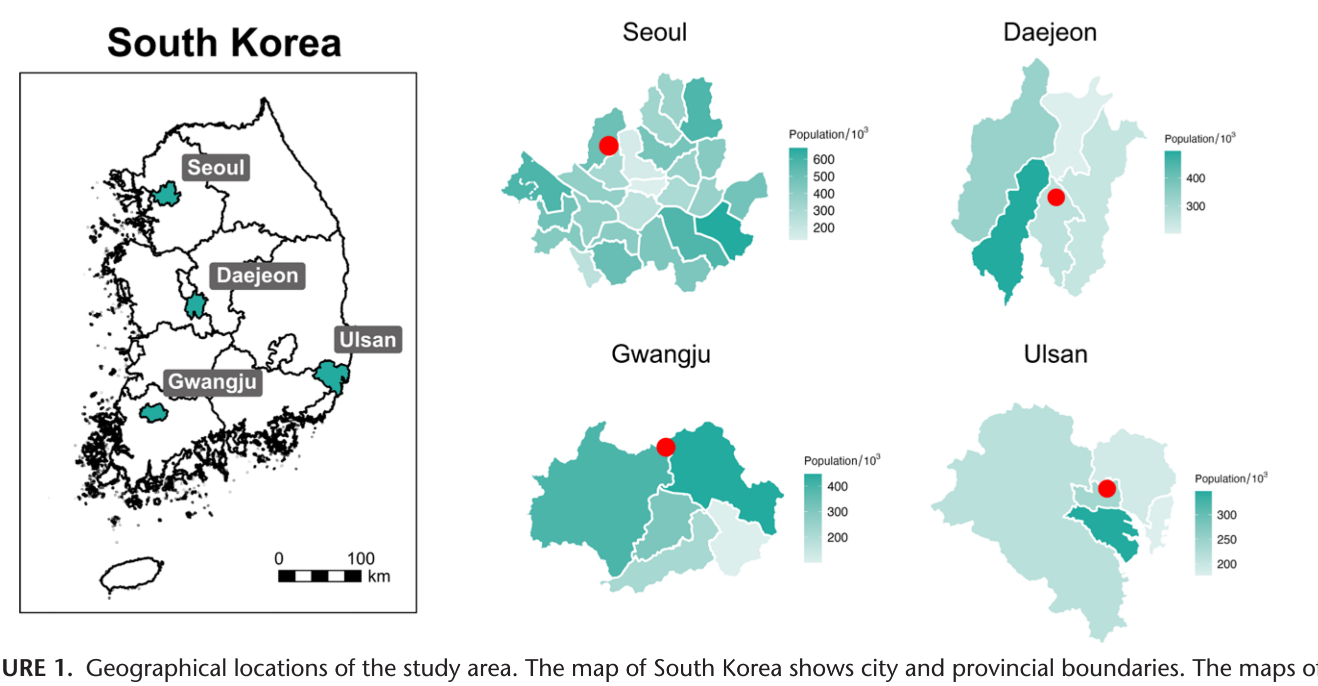

FIGURE 1. Geographical locations of the study area. The map of South Korea shows city and provincial boundaries. The maps of the four cities show district boundaries. The red dot indicates the location of the air pollution intensive monitoring station in each city. The green color gradient indicates population density.

collectively account for nearly 30% of the total population in South Korea. The geographical locations of these cities are shown in Figure 1. We implemented several exclusion criteria for the study population: multiple births (e.g., twins); maternal age at birth <14 or >50 years; gestational period <22 weeks or >44 weeks; birth weight <1 kg or >5 kg; and missing information on infant's sex, maternal marital status, education level, or occupation, or paternal education level or birth order.

PTB was defined by a gestational period of <37 weeks. Infants with birth weight <2.5 kg were classified as LBW, and infants with birth weight <10th percentile value for their respective gestational age and sex were classified as SGA. The cutoff values for SGA were derived from a previous study on the distribution of newborn birth weights in South Korea (eTable 1; http://links.lww.com/EDE/C239).[18] For under-5 mortality, we identified deaths from any cause before reaching the age of 5.

Ethics approval was not required for this study, as the data consisted of deidentified secondary data released for research purposes.

Exposure Assessment

We obtained hourly measurements of $PM_{2.5}$ and its chemical components, spanning from 2012 to 2015, from the National Institute of Environmental Research, a subsidiary of the Ministry of Environment, South Korea. These data were measured from four stations, designated as air pollution intensive monitoring stations by the ministry, one in each of the four cities. The air pollution monitoring station in Ulsan commenced operations in 2014; therefore, we excluded infants who were conceived in Ulsan during the years 2012–2013 from the study. Along with $PM_{2.5}$ total mass, the data included concentrations of 25 distinct components: organic carbon (OC), elemental carbon (EC), sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), chloride (Cl^-), potassium cation (K^+), sodium (Na^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), iron (Fe), manganese (Mn), titanium (Ti), zinc (Zn), lead (Pb), copper (Cu), vanadium (V), nickel (Ni), arsenic (As), selenium (Se), chromium (Cr), sulfur (S), potassium (K), calcium (Ca), and bromine (Br). Further details on the $PM_{2.5}$ and its components data can be found elsewhere.[19] The present study focused on the five major components (OC and EC as carbonaceous compounds, and SO_4^{2-}, NO_3^-, and NH_4^+ as the group of secondary inorganic aerosols) and five inorganic ions (Cl^-, K^+, Na^+, Mg^{2+}, and Ca^{2+}) associated with sea salts.[20] Using the hourly data, we calculated the daily 24-hour mean concentrations for each pollutant. We note that the 15 components not included in the analysis had missing daily concentrations for more than 25% of the study period.

We obtained daily mean temperature data for the same time period as the $PM_{2.5}$ data, measured by the automated synoptic observing system of the Korea Meteorological Administration. These temperature measurements were also collected at a single monitoring station in each of the four cities.

For each birth, we calculated the average exposure levels for each pollutant and temperature over the entire pregnancy, as well as for each trimester (1–13 weeks, 14–26 weeks, and 27 weeks to delivery). The exposures were assigned based on the city of residence at the time of the infant's birth. Births were excluded from the analysis of a pollutant and trimester if data were missing for more than 25% of the weeks for that specific pollutant and trimester.

Statistical Analysis

We employed logistic regression models in which we individually included in separate models each pair of pollutants ($PM_{2.5}$ and its components) and outcome variables (PTB, LBW, SGA, and under-5 mortality). Based on previous literature, we selected covariates suggested as potential confounders in the association between $PM_{2.5}$ and adverse birth outcomes.[16,21,22] For all outcomes, we adjusted for the following covariates: infant's sex (male or female), maternal age (<25, 25–29, 30–34, or >34 years), maternal occupation (nonmanual, manual, or unemployed), maternal and paternal education level (middle school or lower, high school, college or higher), maternal marital status (married or unmarried), birth order (first, second, third, or higher), year and season of conception, indicator variable for city, and temperature (as a continuous variable). For LBW, we further adjusted for gestational week as a continuous variable. For under-5 mortality, we made additional adjustments for both gestational week and birth weight, treated as continuous variables. We estimated trimester-specific effects using models that simultaneously included exposure levels for each trimester.

Several sensitivity analyses were conducted. First, we made separate additional adjustments for the concentration of all other components ($PM_{2.5}$ total mass − component of interest) when examining the effect of each component exposure. Second, considering the potential correlation between exposures across different trimesters, we modified our approach for estimating trimester-specific effects. When examining the effect of exposure for a particular reference trimester, we adjusted for the residuals of the predicted exposures for the remaining two trimesters, based on the exposure levels for the reference trimester. This methodological approach is described in more detail in a previous study.[23] Additionally, we estimated trimester-specific effects by including exposure level for a single trimester in the model at a time. Third, the study subjects were limited to term births (gestational period ≥37 weeks) when examining outcomes for LBW, SGA, and under-5 mortality. Fourth, infant mortality was analyzed instead of under-5 mortality. Last, we used monthly predicted $PM_{2.5}$ total mass concentrations at the district level for exposure assessment. The prediction model was developed by the AiMS-CREATE (Ai-Machine learning and Statistics Collaborative Research Ensemble for Air pollution, Temperature, and all types of

Environmental exposure) team in South Korea. The details of the model have been described previously[24] and are also available in eAppendix 1; http://links.lww.com/EDE/C239. Based on this data, we obtained monthly $PM_{2.5}$ concentrations aggregated at the district level. These concentrations were linked to birth data based on the month of birth and the district of residence at the time of birth. Average exposures for each trimester were calculated based on the month corresponding to each week of gestation. Modeled data on individual components were not available.

To explore potential effect modification by infant's sex, maternal age, and maternal education level, we included a multiplicative interaction term between $PM_{2.5}$ total mass exposure and each of these variables in the model, individually. We stratified the models by these variables to obtain strata-specific estimates. For under-5 mortality, we also assessed potential effect modification by PTB, LBW, and SGA.

Data construction was performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and statistical analyses were performed using R software 4.3.0 (The R Development Core Team, Vienna, Austria).

RESULTS

Out of the total 1,310,310 births recorded nationwide from 2013 to 2015, 365,134 occurred in the study cities. After applying the exclusion criteria, we included 324,566 infants in the analysis. The characteristics of the study population are shown in Table 1. Among all births, 4.4% were preterm, 3.5% had low birth weight, 6.7% were categorized as small for gestational age, and 0.2% died before reaching the age of 5. While we did not include paternal age in the analysis, it had a correlation of 0.61 with maternal age. The majority of parents had an educational level of college or higher, yet the correlation between maternal and paternal educational levels was moderate (Cramér's V=0.38). The characteristics of the term births are given in eTable 2; http://links.lww.com/EDE/C239.

Table 2 provides summary statistics for prenatal exposures to each pollutant across all study areas, and eTable 3; http://links.lww.com/EDE/C239 shows these exposures by city. The average $PM_{2.5}$ exposure during the study period was 33.46 μg/m³, which exceeded the Korean annual standard of 25 μg/m³ that was in place at the time. Following revisions in 2018, the current annual standard for $PM_{2.5}$ in Korea has been lowered to 15 μg/m³. The 10 components included in the analysis constituted approximately 70% of the total $PM_{2.5}$ mass concentration. Table 3 presents the correlations between pollutants for the entire pregnancy exposure. $PM_{2.5}$ exposure was highly correlated with several individual components, such as EC and NO_3^-. Some component pairs, such as NO_3^- and NH_4^+, or Mg^{2+} and Ca^{2+}, exhibited strong correlations (r >0.9). The correlations among trimester-specific $PM_{2.5}$ exposures were low, with an absolute correlation coefficient of less than 0.3 (eTable 4; http://links.lww.com/EDE/C239).

TABLE 1. Characteristics of the Study Population (n = 324,566)

Characteristic	
Length of gestation (weeks), mean ± SD	38.80 ± 1.42
22–26, n (%)	36 (0.01)
27–36, n (%)	14,141 (4.4)
≥37 (term birth), n (%)	310,389 (95.6)
Birth weight (kg), mean ± SD	3.24 ± 0.42
<2.5 (low birth weight), n (%)	11,435 (3.5)
≥2.5, n (%)	313,131 (96.5)
Small for gestational age, n (%)	21,840 (6.7)
Death under 5 years, n (%)	490 (0.2)
Infant sex, n (%)	
Male	166,537 (51.3)
Female	158,013 (48.7)
Marital status, n (%)	
Married	321,202 (99.0)
Single	3,348 (1.0)
Maternal age (years), mean ± SD	31.96 ± 3.89
<25, n (%)	11,605 (3.6)
25–29, n (%)	64,963 (20.0)
30–34, n (%)	171,320 (52.8)
>34, n (%)	76,662 (23.6)
Maternal occupation, n (%)	
White-collar	127,106 (39.2)
Blue-collar	21,912 (6.8)
Unemployed	175,532 (54.1)
Maternal education, n (%)	
Middle school or lower	3,292 (1.0)
High school	55,051 (17.0)
College or higher	266,207 (82.0)
Paternal education, n (%)	
Middle school or lower	3,259 (1.0)
High school	56,998 (17.6)
College or higher	264,293 (81.4)
Birth order, n (%)	
First	184,121 (56.7)
Second	116,113 (35.8)
Third or higher	24,316 (7.5)
Birth region, n (%)	
Seoul	235,675 (72.6)
Daejeon	35,710 (11.0)
Gwangju	39,432 (12.1)
Ulsan	13,733 (4.2)
Year of conception, n (%)	
2012	79,942 (24.6)
2013	103,974 (32.0)
2014	114,088 (35.2)
2015	26,546 (8.2)
Season of conception, n (%)	
Winter	78,635 (24.2)
Spring	82,496 (25.4)
Summer	84,887 (26.2)
Fall	78,532 (24.2)

Odds ratios (ORs) and 95% confidence intervals (CIs) for birth outcomes and under-5 mortality associated with interquartile range width (IQRw) increase in exposure to $PM_{2.5}$ and its components are shown in Figure 2. The numerical effect estimates corresponding to Figure 2 are available in eTable 5; http://links.lww.com/EDE/C239. An IQR (8.5 μg/m³) increase in $PM_{2.5}$ exposure during the entire pregnancy was positively associated with increased risk of PTB (OR = 1.17; 95% CI = 1.11, 1.23), while the associations with LBW, SGA, and under-5 mortality were close to null. The effect estimates for exposure to $PM_{2.5}$ during the 3rd trimester on LBW, SGA, and under-5 mortality indicated positive associations. For PTB, the effect estimates for the 2nd and 3rd trimester exposure were higher than those for the 1st trimester. Effect estimates were generally consistent across components, though some variation was observed for PTB. Notably, exposure to EC during the entire pregnancy was associated with a higher risk of PTB compared with other components.

In the sensitivity analyses, additional adjustments for the concentration of all other components in the models for individual components led to minor changes in the effect estimates (eTable 6; http://links.lww.com/EDE/C239). Sensitivity analyses for the trimester-specific effects (eTable 7; http://links.lww.com/EDE/C239), limiting the study population to term births (eTable 8; http://links.lww.com/EDE/C239), and changing the outcome from under-5 mortality to infant mortality (eTable 9; http://links.lww.com/EDE/C239) also did not substantially change the results. The exposure levels of modeled $PM_{2.5}$ are given in eTable 10; http://links.lww.com/EDE/C239. Although the overall absolute level of exposure to modeled $PM_{2.5}$ was lower than that of monitored $PM_{2.5}$, the correlation between them in each city was moderate (mostly r >0.6) for exposure throughout the entire pregnancy and was high (mostly r >0.8) for trimester-specific exposures. The association of $PM_{2.5}$ exposure based on modeling data with each health outcome led to slight changes in effect estimates compared with those based on monitoring data, yet overall results remained consistent (eTable 11; http://links.lww.com/EDE/C239).

We tested effect modification by infant's sex, maternal age, and maternal education level for the association between

TABLE 2. Descriptive Statistics of Prenatal Exposure to $PM_{2.5}$ and its Components

	Entire Pregnancy		1st Trimester		2nd Trimester		3rd Trimester	
	Mean ± SD	IQRw	Mean ± SD	IQRw	Mean ± SD	IQRw	Mean ± SD	IQRw
$PM_{2.5}$	33.46 ± 5.21	8.50	33.90 ± 8.50	12.70	33.67 ± 8.56	13.70	34.15 ± 8.25	13.68
OC	3.90 ± 0.75	0.71	3.76 ± 1.16	1.56	3.86 ± 1.15	1.49	4.00 ± 1.12	1.37
EC	1.57 ± 0.29	0.35	1.54 ± 0.38	0.60	1.56 ± 0.39	0.59	1.55 ± 0.41	0.65
SO_4^{2-}	6.47 ± 1.87	3.32	6.62 ± 2.53	4.40	6.35 ± 2.49	3.85	6.47 ± 2.45	3.70
NO_3^-	6.37 ± 2.20	3.99	6.37 ± 3.00	4.79	6.30 ± 3.06	5.02	6.38 ± 3.07	4.83
NH_4^+	4.11 ± 0.99	1.62	4.13 ± 1.36	2.05	4.04 ± 1.37	2.11	4.15 ± 1.32	2.00
Cl^-	0.43 ± 0.13	0.22	0.43 ± 0.26	0.42	0.42 ± 0.26	0.44	0.42 ± 0.28	0.48
K^+	0.17 ± 0.05	0.06	0.17 ± 0.09	0.13	0.17 ± 0.09	0.13	0.17 ± 0.09	0.14
Na^+	0.17 ± 0.03	0.03	0.17 ± 0.05	0.05	0.16 ± 0.05	0.05	0.17 ± 0.05	0.06
Mg^{2+}	0.09 ± 0.09	0.14	0.09 ± 0.10	0.10	0.09 ± 0.10	0.11	0.09 ± 0.11	0.11
Ca^{2+}	0.24 ± 0.20	0.36	0.24 ± 0.25	0.30	0.24 ± 0.26	0.31	0.23 ± 0.26	0.32

IQRw, interquartile range width; SD, standard deviation.

TABLE 3. Correlation Coefficients Between Prenatal Exposures to $PM_{2.5}$ and Its Components

	$PM_{2.5}$	OC	EC	SO_4^{2-}	NO_3^-	NH_4^+	Cl^-	K^+	Na^+	Mg^{2+}	Ca^{2+}
$PM_{2.5}$	1.00	0.43	0.75	0.69	0.76	0.69	0.64	0.13	−0.12	0.67	0.69
OC		1.00	0.40	−0.29	−0.17	−0.29	0.15	0.64	0.38	−0.21	−0.23
EC			1.00	0.51	0.66	0.46	0.53	0.45	−0.03	0.35	0.41
SO_4^{2-}				1.00	0.87	0.91	0.52	−0.24	−0.07	0.70	0.76
NO_3^-					1.00	0.92	0.66	−0.13	−0.18	0.76	0.81
NH_4^+						1.00	0.59	−0.34	−0.11	0.74	0.79
Cl^-							1.00	0.14	−0.03	0.45	0.45
K^+								1.00	0.07	−0.35	−0.33
Na^+									1.00	−0.11	−0.14
Mg^{2+}										1.00	0.98
Ca^{2+}											1.00

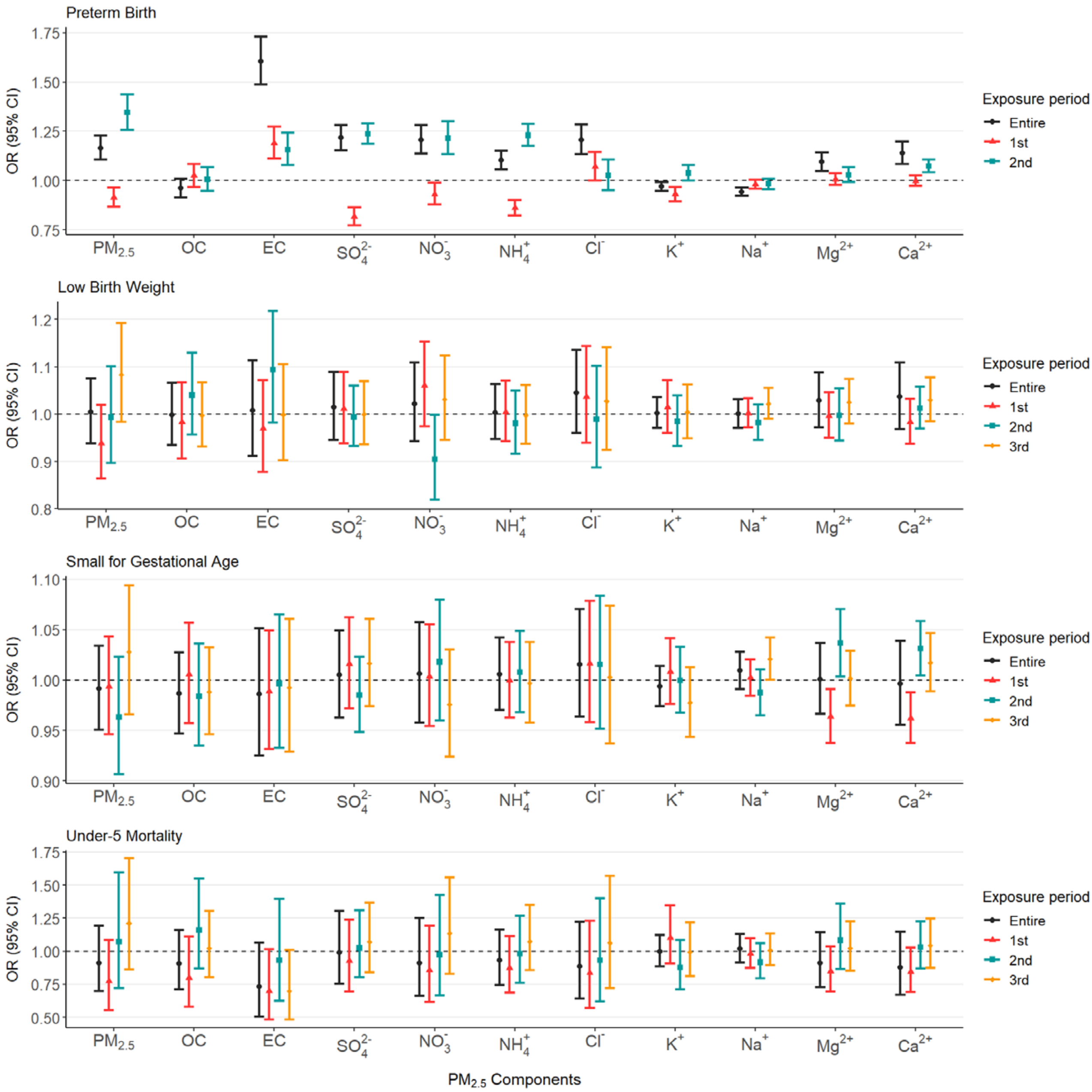

FIGURE 2. Association between prenatal exposure to $PM_{2.5}$ and its components and health outcomes by exposure period. The points indicate the odds ratios (ORs), and the solid vertical lines represent the 95% confidence intervals (CIs) per interquartile range (IQR) increase in each pollutant. Pollutant-specific IQR values for the entire pregnancy were applied to all trimesters. Black color denotes the results for exposure during the entire pregnancy, and red, green, and yellow colors denote results for exposure during the 1st, 2nd, and 3rd trimesters, respectively. The trimester-specific estimates were derived from models that include exposures for all three trimesters.

$PM_{2.5}$ exposure during the entire pregnancy and each outcome (Table 4). We observed higher effect estimates for PTB among female infants compared with male infants. Infants born to mothers younger than 25 years showed the highest effect estimates across all outcomes compared with other age groups. For mothers older than 34 years, effect estimates for PTB and LBW were higher compared with those in the 25–34 age range. Regarding maternal education, a higher effect for PTB was observed in mothers with a high school education compared with mothers with other educational levels, but this pattern was not consistent across the other outcomes. When examining effect modification by PTB, LBW, and SGA for the

TABLE 4. Effect Modification by Infant's Sex, Maternal Age, and Maternal Education Level on the Association Between Prenatal Exposure to $PM_{2.5}$ and Health Outcomes

	Preterm Birth		Low Birth Weight		Small for Gestational Age		Under-5 Mortality	
	OR (95% CI)	$P_{int.}$	OR (95% CI)	$P_{int.}$	OR (95% CI)	$P_{int.}$	OR (95% CI)	$P_{int.}$
Infant's sex								
Male	1.14 (1.05, 1.24)	*ref.*	0.96 (0.85, 1.09)	*ref.*	0.96 (0.90, 1.03)	*ref.*	0.86 (0.56, 1.31)	*ref.*
Female	1.28 (1.16, 1.40)	0.82	1.04 (0.94, 1.16)	0.78	1.02 (0.95, 1.10)	0.76	0.96 (0.60, 1.53)	0.82
Maternal age (years)								
<25	1.38 (1.00, 1.91)	*ref.*	1.32 (0.88, 1.96)	*ref.*	1.19 (0.94, 1.52)	*ref.*	1.36 (0.39, 4.68)	*ref.*
25–29	1.07 (0.93, 1.24)	0.31	0.92 (0.76, 1.10)	0.83	1.00 (0.90, 1.12)	0.87	0.81 (0.40, 1.61)	0.86
30–34	1.19 (1.09, 1.30)	0.49	0.98 (0.87, 1.09)	0.99	0.96 (0.89, 1.03)	0.75	1.07 (0.66, 1.73)	0.81
>34	1.27 (1.13, 1.43)	0.96	1.10 (0.94, 1.28)	0.89	1.02 (0.92, 1.13)	0.80	0.69 (0.38, 1.25)	0.80
Maternal education								
Middle school or lower	1.13 (0.67, 1.90)	*ref.*	1.05 (0.56, 1.96)	*ref.*	0.87 (0.57, 1.33)	*ref.*	1.60 (0.25, 10.36)	*ref.*
High school	1.33 (1.16, 1.52)	0.84	0.95 (0.80, 1.13)	0.85	0.96 (0.85, 1.08)	0.57	0.93 (0.48, 1.81)	0.37
College or higher	1.17 (1.09, 1.26)	0.63	1.02 (0.93, 1.11)	0.95	1.00 (0.94, 1.05)	0.42	0.87 (0.61, 1.26)	0.42

Odds ratios (ORs) and 95% confidence intervals (CIs) calculated per 10 μg/m³ increase in $PM_{2.5}$; adjusted for infant's sex (except when analyzing sex as effect modifier), maternal age (except when analyzing age as effect modifier), maternal education level (except when analyzing education as effect modifier), paternal education level, maternal occupation, marital status, birth order, year and season of conception, indicator variable for city, and temperature.

$P_{int.}$ represents P value for interaction term between $PM_{2.5}$ and each effect modifier.

association between $PM_{2.5}$ and under-5 mortality, we found no notable differences between subgroups (eTable 12; http://links.lww.com/EDE/C239).

DISCUSSION

To the best of our knowledge, this is the first study to explore the association between prenatal exposure to $PM_{2.5}$ components and infant health outcomes in South Korea. We found that exposure to $PM_{2.5}$ during the entire pregnancy was positively associated with increased risk of PTB, but not with LBW, SGA, or under-5 mortality. Among the components, EC showed higher effect estimates than other components for PTB, a finding that remained robust after adjusting for the concentration of all other components.

There is a strong body of evidence indicating that $PM_{2.5}$ exposure is linked to adverse birth outcomes. Several systematic review and meta-analysis studies showed increased risks of PTB, LBW, and SGA associated with $PM_{2.5}$ exposure.[11,25–28] Ju et al.[11] reported that the overall relative risks (RRs) per 10 μg/m³ increase in $PM_{2.5}$ exposure during the entire pregnancy were 1.093 (95% CI = 1.064, 1.122) for PTB, 1.083 (95% CI = 1.038, 1.130) for term LBW, and 1.101 (95% CI = 1.057, 1.148) for SGA. Studies conducted in South Korea also indicated consistent associations between PM_{10} and adverse birth outcomes.[21,29–33] Our results align with previous research in terms of the increased risks of PTB associated with $PM_{2.5}$ exposure. No positive association was found between $PM_{2.5}$ exposure during the entire pregnancy and LBW or SGA; however, positive associations were observed for 3rd trimester exposures. Possible underlying mechanisms linking $PM_{2.5}$ to adverse birth outcomes include oxidative stress, DNA methylation, and endocrine disruptions. Increased inflammation in the mother could adversely affect placental function, impairing the supply of nutrients and oxygen to the fetus.[10,34]

The existing evidence also supports the hypothesis that exposure to $PM_{2.5}$ is associated with early childhood mortality. Previous systematic reviews suggested that $PM_{2.5}$ exposure is associated with infant or under-5 mortality.[12,35] Nevertheless, most studies cited in these reviews focused on postnatal exposures, leaving a gap in the literature concerning prenatal exposure. In South Korea, Son et al.[22] and Jung et al.[36] reported an increased risk for infant mortality associated with $PM_{2.5}$. Our study found a suggestive association of $PM_{2.5}$ in the 3rd trimester with under-5 mortality, and this pattern remained consistent when we shifted the outcome from under-5 mortality to infant mortality (eTable 9; http://links.lww.com/EDE/C239). The observed effect of the 3rd trimester exposure may be partially due to its correlation with early postnatal exposure, which could influence infant and child mortality.[37] Additionally, prenatal exposure to $PM_{2.5}$ can impact early life mortality beyond the initial adverse birth outcomes through mechanisms such as impairing lung development and weakening the immune system. These changes can increase the susceptibility of infants to respiratory infections, which can be fatal.[38–40]

Compared with the total mass of $PM_{2.5}$ exposure, evidence for the effects of individual chemical components of $PM_{2.5}$ on birth outcomes has been less consistent between studies. A previous study of meta-analysis found that components including EC, Zn, and Ti, had higher effects on LBW compared with other components.[41] A study conducted in California, USA found positive associations between PTB and various components, including NO_3^-, NH_4^+, EC, and OC.[17] A study conducted in China indicated that black carbon (BC),

SO_4^{2-}, NH_4^+, and NO_3^- were associated with higher effect estimates for PTB.[42]

PM is a chemically complex substance, and each of its components may influence health outcomes through various biological pathways.[43] Carbonaceous compounds, EC and OC, are derived from combustion sources such as traffic and biomass burning.[44] This study found an association of PTB with EC, but not with OC. A previous study reported that exposure to BC, often represented by EC, was associated with reduced DNA methylation, leading to oxidative stress and atherosclerosis.[45] However, carbon particles may act as cores for adsorbed chemical species, such as endotoxins, complicating the toxicologic interpretation of responses to carbonaceous materials.[43] In our study, PTB was also associated with secondary inorganic aerosols, which are indirectly formed from gaseous precursors originating from sources including fossil fuel combustion and biogenic activities. Toxicologic studies suggested that secondary inorganic components could induce a pulmonary inflammatory response, potentially due to the acidity of the exposure, though findings were not consistent across studies.[46] Among the sea salt-related inorganic ions, Cl^-, Mg^{2+}, and Ca^{2+} showed positive associations with PTB, while K^+ and Na^+ did not. These results might not directly stem from the components themselves but could be related to their association with other pollutants or exposures from related sources that were not accounted for in this study. Components from sea salt are generally considered less toxic, yet their contamination with other materials could introduce various chemical species that modify toxicity.[46] Additionally, sea salt may be less well represented in our study, which primarily includes inland metropolitan cities. Our findings suggest that the effects of individual components may vary, even among those sharing similar sources.

In this study, we observed that exposure to $PM_{2.5}$ during later trimesters exhibited higher effect estimates compared with exposures in earlier trimesters. While the correlations in exposure between trimesters were low, our sensitivity analysis, which accounted for covariance among trimester exposures, yielded consistent results. However, identifying a definitive critical window for exposure was challenging because the trimesters associated with the highest effect estimates varied depending on the specific $PM_{2.5}$ component, and most results were not substantially different. Additionally, PTB showed larger variations in effect estimates between trimesters compared with other outcomes. This may be because gestational week distinctly defines preterm and term births, and infants born preterm do not experience full third-trimester exposure. Therefore, the trimester-specific results for PTB should be interpreted with caution. Previous systematic reviews and meta-analyses also have provided mixed findings on critical exposure time windows.[11,26,27] Several mechanisms have been proposed to explain why early or late pregnancy might serve as critical periods for exposure;[47–49] however, additional research is required to establish evidence for the most susceptible time window(s) and elucidate the underlying biological mechanisms.

One limitation of our study is the potential for exposure misclassification. We used a single monitoring station in each city to estimate exposure, failing to account for the spatial heterogeneity of pollutants within the city. To address this, we used modeled $PM_{2.5}$ concentration at the district level for sensitivity analysis and found consistent results. The modeled $PM_{2.5}$ demonstrated a high correlation between districts ($r > 0.9$) within each city (eFigure 1; http://links.lww.com/EDE/C239), indicating relatively low spatial variation. However, modeled data for individual components were not available, so we obtained additional data from the $PM_{2.5}$ chemical speciation monitoring network in South Korea. This network operates two stations in each of the four cities in our study area, with one station located at the exact same point as the intensive monitoring station (eFigure 2; http://links.lww.com/EDE/C239). Data from the chemical speciation monitoring stations, however, were only available from 2015 to 2019, not covering our study period (2012–2015). To explore potential spatial variability for components, we calculated the correlation coefficients of daily concentrations for each component at the two monitoring stations within each city (eFigure 3; http://links.lww.com/EDE/C239). These results suggest that the extent of exposure misclassification may differ across components,[50,51] and may explain some but not all differences in observed associations across components. Furthermore, we based our exposure estimates on the city of residence at the time of birth, without incorporating the exact address, outdoor activity patterns, or residential mobility during pregnancy. Nonetheless, previous studies conducted in the United States showed that distances moved during pregnancy were generally short (<10 km), and accounting for residential mobility did not significantly change the estimated effects of air pollution exposure during pregnancy.[52–54] The overall proportion of women aged between 15 and 50 years moving out of their city in South Korea during the study period was below 10%,[55] although this may differ for pregnant women. Another limitation is that we could not analyze many trace components such as Pb, Zn, and Ni due to a high percentage of missing data. While these elements constitute a marginal portion of the total $PM_{2.5}$ mass, previous studies have suggested they may pose substantial health risks.[56,57]

Regarding birth certificate data, we lacked information on several potential confounding factors, such as tobacco and alcohol consumption, prenatal care, and maternal physical activity. However, previous research showed that adjusting for maternal smoking did not substantially change the effect estimates of air pollution on infant mortality and low birth weight, suggesting that smoking may not be an important confounder.[58,59] In addition, tobacco use among Korean women is notably lower than that of many other countries.[60–63] Moreover, information on tobacco and alcohol use, even when available, tends to be underreported in birth certificates.[64]

In conclusion, this study provides supportive evidence for the adverse effects of $PM_{2.5}$ and its components on birth outcomes, particularly PTB, in metropolitan areas of South Korea. We found that certain chemical components of $PM_{2.5}$, such as EC, were more highly associated with PTB. Further evidence on which components of $PM_{2.5}$ present greater health risks could facilitate the identification of particularly harmful $PM_{2.5}$ sources. Such insights would enable policymakers to devise more focused public health strategies, including the development of interventions tailored to local emission profiles.

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