

Different effects of PM₁₀ exposure on preterm birth by gestational period estimated from time-dependent survival analyses

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Abstract

Purpose We conducted this study to determine if the preterm risks due to PM₁₀ exposure vary with the exposure periods during pregnancy. This study was also conducted to estimate the different effects of PM₁₀ exposure on preterm birth by exposure periods using the extended Cox model with PM₁₀ exposure as a time-dependent covariate. **Methods** We studied birth data obtained from the Korea National Statistical office for 374,167 subjects who were delivered between 1998 and 2000 in Seoul, South Korea. We used PM₁₀ data that was measured hourly to give 24-h

averages at 27 monitoring stations in Seoul. The extended Cox model with time-dependent exposure was used to determine if the risk of preterm delivery could be associated with PM₁₀ exposures for each trimester during pregnancy.

Results Effect of PM₁₀ exposure prior to the 37 weeks of gestational period was stronger on the risk of premature birth than that posterior to the 37 weeks of gestational weeks. This trend was consistent for each trimester; however, the hazard ratios for preterm delivery associated with PM₁₀ exposure in the first and third trimester were slightly higher than those of the second trimester.

Conclusions The risk of preterm birth associated with exposure to PM₁₀ differed with the exposure period of the neonates. Therefore, when studying the impact of air pollution exposure during pregnancy, the exposure period during pregnancy should be considered.

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Introduction

Gestational age, infant birth weight and growth of the fetus may have an effect on perinatal health. In addition, perinatal death, infant mortality, and illnesses in adults can all be caused by preterm birth, which is defined as delivery prior to 37 weeks of pregnancy (Joseph and Kramer 1996). Many studies have shown that environmental factors, including cigarette smoking (Horta et al. 1997; Cnattingius et al. 2006; Raatikainen et al. 2007), environmental tobacco smoke (ETS) (Windham et al. 2000; Kharrazi et al. 2004), organic solvents (Wang et al. 2000; Ha et al. 2002), and alcohol consumption can contribute to preterm

delivery (Albertsen et al. 2004). The relationship between birth outcomes and air pollution exposure has also been examined in many epidemiological studies that have been conducted to evaluate factors including total suspended particulates (TSP) (Wang et al. 1997; Bobak and Leon 1999; Bobak 2000; Ha et al. 2001), sulfur dioxide (SO₂) (Wang et al. 1997; Bobak and Leon 1999; Bobak 2000; Ha et al. 2001; Maisonet et al. 2001), carbon monoxide (CO) (Ha et al. 2001; Maisonet et al. 2001; Ritz and Yu 1999; Medeiros and Gouveia 2005; Salam et al. 2005), ozone (O₃) (Salam et al. 2005; Hansen et al. 2006), nitrogen dioxide (NO₂) (Ha et al. 2001; Medeiros and Gouveia 2005), and particulate matter <10 μm (PM₁₀) (Bobak and Leon 1999; Medeiros and Gouveia 2005; Hansen et al. 2006; Dejmeek et al. 1999; Ritz et al. 2000; Ha et al. 2003; Rogers and Dunlop 2006; Leem et al. 2006). In a previous study that we conducted in Seoul, South Korea, exposure to air pollution during pregnancy was found to be significantly associated with the occurrence of preterm birth (Ha et al. 2004).

The association of premature delivery with air pollution exposure during pregnancy has been investigated using various statistical approaches that can be classified as community- or individual-based. In studies that use a community-based approach, a time-series analysis based on a Poisson regression model is commonly used to find the increment of preterm delivery due to air pollution exposure (Anderson et al. 2001; Roberts 2004; Roberts 2005; Peng et al. 2005; Sagiv et al. 2005). However, because the population-based approach assumes that the population contains homogeneous characteristics for the entire study period, it is difficult to use individual-based confounders that vary with time. Therefore, the individual-based approach has become more popular. This approach has generally involved the use of a logistic regression model in which the distribution of predictors is compared in women that experienced preterm birth and those who carried their child to term (Bobak 2000; Hansen et al. 2006; Ritz et al. 2000; Ha et al. 2004; Xu et al. 1995; Marozienne and Grazuleviciene 2002; Yang et al. 2002; Yang et al. 2003; Tsai et al. 2003; Woodruff et al. 2003; Liu et al. 2003; Wilhelm and Ritz 2005). For studies in which a quantitative outcome, such as gestational age or fetal growth associated with air pollution exposure is required, a linear regression analysis approach has commonly been performed (Xu et al. 1995; Hansen et al. 2007).

In a previously conducted study, we compared the results obtained when logistic regression and Cox proportional hazards models were used to investigate the relationship between pollution and preterm birth in South Korea (Ha et al. 2004). In the present study, which was conducted to determine if the risk for a preterm birth due to

air pollution exposure varied with gestational age, we used the extended Cox model, after accounting for the time-dependent covariate. We then compared the results from (1) the conventional individual-based logistic regression analysis, (2) the conventional regression analysis, (3) the Cox proportional hazards model, and (4) the extended Cox model with time-dependent exposure to determine the usefulness of the time-to-event analysis rather than conventional approaches in the study of preterm delivery due to exposure to air pollution, such as PM₁₀, in pregnant Korean women.

Materials and methods

Population and data collection

Birth data containing information such as the gender and weight of the infant, parental age, education and occupation, parity, birth order, gestational age, marital status, birth date, place of birth and history of delivery were obtained from the Korea National Statistical Office. Only subjects who were delivered between January 1, 1998 and December 31, 2000 in Seoul, South Korea were included in this study. The confounding factors to be controlled in this study were the gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, and month and day of the week at birth. Subjects who were born before 25 weeks or after 41 weeks of gestation were excluded, as were subjects who were delivered as multiple neonates. Finally 374,167 individuals were included in our analysis. The prevalence of preterm birth (before 37 weeks of gestation) in the subjects was 3.3% ($N = 12,153$).

Air pollution data

We obtained PM₁₀ data, which was measured hourly to give 24-h averages at 27 monitoring stations in Seoul, from the National Institute of Environmental Research. We ruled out exposure data when there was a PM₁₀ of $\geq 200 \mu\text{g}/\text{m}^3$ because these data may have been influenced by dust and sand storms in Mongolia or China. The air pollution exposure for each participant, based on the averaged exposure at 27 monitoring stations in Seoul, gestational age and delivery date, was then calculated for the first, second and third trimester. Each trimester was defined as 3 calendar months. Exposure during third trimester corresponded to the averaged exposure for a period from 186 days of gestation to birth. Infants with gestational duration less than 186 days have missing values for the third trimester exposure.

Statistical analysis

As a preliminary study, we investigated the relationship between preterm delivery and covariates, such as the gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth and month and day of the week at birth using χ^2 test or t test. We then evaluated the impact of PM_{10} exposure during each trimester to determine the risk of preterm birth and reduced pregnancy period using conventional statistical approaches, such as multiple logistic regression and multiple linear regression analyses, respectively, after adjusting for confounding factors and a continuous effect of a linear long-term trend. Odds ratios and regression coefficients were estimated for preterm delivery according to the increase of averaged interquartile range (IQR) of PM_{10} concentration levels in each trimester during pregnancy using the fitted logistic regression and regression models, respectively. As an alternative approach, we first performed Cox proportional hazards regression analysis, after adjusting for confounding factors and a continuous effect of long-term trend, on preterm delivery and estimated the hazard ratios for preterm birth according to the increase of averaged IQR of PM_{10} concentration levels in each trimester during pregnancy. We considered preterm delivery as an event and subject with a term birth as censoring in the Cox regression model. We censored the term births after 37 weeks of pregnancy at 38 gestational weeks in the Cox proportional hazards model (not at the date of birth). That is, the time variable of the Cox proportional hazards model was set to 38 for the term births after 37 weeks. Tied data were controlled by Breslow's approximation. We next analyzed the data using an extended Cox model with time-dependent exposure, which permits nonproportional hazards, managing for a time-dependent covariate of PM_{10} exposure during each trimester by adding a product term on time function (Kleinbaum and Klein 2005). The statistical model for the extended Cox model with time-dependent exposure in this study was as follows: $h(t|X(t)) = h_0(t) \exp[\sum_{i=1}^p \beta_i X_i + \delta_1 X_1 g_1(t)]$ for gestational age, t . In this equation, $h_0(t)$ is a baseline hazard function as all covariates are zero, X_i ($i = 2, \dots, p$) is the i th time-independent covariate, and $X_1 \times g_1(t)$ is a product term where $g_1(t)$ is a function of t for X_1 , which is a time-dependent covariate of PM_{10} exposure during each trimester. We first tried the extended Cox model containing dummy variables for different time periods. As a result, since the outcomes for different time periods showed linearity, we considered $g_1(t)$ as a linear indicator function in this study. That is, we considered $g_1(t)$ to be 1 if $t < 32$; 3 if $32 \leq t < 37$; 5 if $t = 37$; and 7 if $t > 37$. So, the corresponding hazard ratios per IQR of X_1 were estimated by $HR = \exp[\text{IQR}(\hat{\beta}_1 + \hat{\delta}_1)]$

if $t < 32$; $HR = \exp[\text{IQR}(\hat{\beta}_1 + 3\hat{\delta}_1)]$ if $32 \leq t < 37$; $HR = \exp[\text{IQR}(\hat{\beta}_1 + 5\hat{\delta}_1)]$ if $t = 37$; $HR = \exp[\text{IQR}(\hat{\beta}_1 + 7\hat{\delta}_1)]$ if $t > 37$ where $\hat{\beta}_1$ and $\hat{\delta}_1$ are estimated coefficients for X_1 and $X_1 g_1(t)$, respectively. All statistical analyses were conducted using SAS (version 8.2, SAS institute, Cary, NC).

Results

Table 1 shows the distribution of the demographic characteristics of the subjects included in this study. The neonates in the preterm group and those in the control group differed by either gender or birth order ($P < 0.0001$ by χ^2 test). In addition, the prevalence of preterm birth of male newborns (3.5%) was higher than that of female newborns (3.0%), and the prevalence of preterm birth increased as birth order increased. Further, fathers who carried their baby to preterm tended to be less educated than those who carried their baby to term ($P < 0.001$ by χ^2 test), and there were also significant differences in maternal age, marital status, maternal history of stillbirth, and month and day of the week at birth between the preterm and control group, respectively ($P < 0.0001$ by t test or χ^2 test). Additionally, the preterm birth rate of single mothers (5.3%) was much higher than that of married mothers (3.2%). Furthermore, the occurrence of a previous stillbirth had a strong impact on the occurrence of preterm birth (7.4%). However, the preterm and control group did not differ when maternal occupation was considered ($P > 0.1$ by χ^2 test). There were 1,471 neonates in the early preterm group (25–31 weeks of gestation), 10,682 in the preterm group having 32–36 weeks of gestation, 13,585 in the control group having 37 week of gestation, and 348,429 in the group having 38–41 weeks of gestation.

Table 2 shows the distribution of PM_{10} concentration levels according to trimester. The exposure levels of PM_{10} were almost the same among the three different periods during pregnancy, and the mean IQR of PM_{10} concentration levels of all three trimesters during pregnancy was $16.53 \mu\text{g}/\text{m}^3$.

We initially evaluated the risks for preterm delivery according to $16.53 \mu\text{g}/\text{m}^3$ (averaged IQR) increase of PM_{10} exposure level during pregnancy using a logistic regression model for preterm birth, after adjusting for confounding factors and a long-term trend effect (Table 3). The results showed that, when the impact of PM_{10} exposure on the risk for preterm delivery according to trimester was evaluated, the risks for preterm birth attributed to the PM_{10} exposures were significantly higher in the third trimester. To verify that the effect of PM_{10} exposures on the risk of preterm delivery according to trimester differed by gestational age, we performed a further analysis according to the

Table 1 Distribution of study population characteristics in women who experienced preterm delivery and normal controls in Seoul, 1998–2000

	<i>N</i> (%)		<i>P</i> value ^a	Prevalence (%)
	Preterm	Control		
Infant's gender			<0.0001	
Male	6,851 (56.4)	187,933 (51.9)		3.5
Female	5,302 (43.6)	174,081 (48.1)		3.0
Maternal age (mean ± SD, years)	29.1 ± 4.1	28.3 ± 3.6	<0.0001	
Paternal education (years)			0.0003	
≤12	5,614 (46.2)	161,164 (44.5)		3.4
>12	6,539 (53.8)	200,850 (55.5)		3.2
Marital status			<0.0001	
Single	95 (0.8)	1,712 (0.5)		5.3
Married	12,058 (99.2)	360,302 (99.5)		3.2
Birth order			<0.0001	
First	6,283 (51.7)	195,437 (54.0)		3.1
Second	4,913 (40.4)	142,615 (39.4)		3.3
Third	878 (7.2)	22,412 (6.2)		3.8
Fourth	66 (0.5)	1,375 (0.4)		4.6
Greater than or equal to fifth	13 (0.1)	175 (0.1)		6.9
Maternal occupation during pregnancy			0.568	
Yes	507 (4.2)	14,726 (4.1)		3.3
No	11,646 (95.8)	347,288 (95.9)		3.2
Maternal history of stillbirth			<0.0001	
Yes	169 (1.4)	2,129 (0.6)		7.4
No	11,984 (98.6)	359,885 (99.4)		3.2
Month of birth			<0.0001	
January	1,186 (9.8)	34,467 (9.5)		3.3
February	1,046 (8.6)	31,963 (8.8)		3.2
March	992 (8.2)	34,135 (9.4)		2.8
April	873 (7.2)	30,879 (8.5)		2.8
May	928 (7.6)	29,842 (8.2)		3.0
June	1,004 (8.3)	27,158 (7.5)		3.6
July	1,002 (8.2)	27,951 (7.7)		3.5
August	1,044 (8.6)	28,085 (7.8)		3.6
September	997 (8.2)	29,999 (8.3)		3.2
October	971 (8.0)	30,460 (8.4)		3.1
November	987 (8.1)	28,867 (8.0)		3.3
December	1,123 (9.2)	28,208 (7.8)		3.8
Day of the week at birth			<0.0001	
Sunday	1,245 (10.2)	33,437 (9.2)		3.6
Monday	1,882 (15.5)	58,593 (16.2)		3.1
Tuesday	1,802 (14.8)	56,459 (15.6)		3.1
Wednesday	1,843 (15.2)	54,791 (15.1)		3.3
Thursday	1,809 (14.9)	55,554 (15.4)		3.2
Friday	1,858 (15.3)	57,932 (16.0)		3.1
Saturday	1,714 (14.1)	45,248 (12.5)		3.7
Total	12,153	374,167		3.3

^a *P* value as obtained by χ^2 test, excepting that for maternal age as obtained by *t* test

Table 2 Distribution of PM₁₀ concentration levels (μg/m³) according to pregnancy period of exposure in Seoul, 1998–2000

Period of PM ₁₀ exposure	Mean ± SD	Percentile						IQR
		Min	25th	50th (median)	75th	90th	Max	
First trimester	65.74 ± 11.06	43.78	57.88	65.19	73.25	77.48	94.11	15.37
Second trimester	65.81 ± 12.05	42.57	56.50	66.05	73.78	80.77	96.22	17.27
Third trimester	65.99 ± 11.93	42.57	57.04	66.49	73.99	79.30	96.22	16.95

IQR interquartile range

Table 3 Odds ratios for developing preterm delivery according to PM₁₀ exposure in each trimester during pregnancy in a logistic regression model

Period of PM ₁₀ exposure	OR ^a (95% CI)	Gestational age (weeks) ^b	OR ^c (95% CI)
First trimester	0.91 (0.87–0.96)	<32	0.81 (0.70–0.93)
		32–36	0.93 (0.88–0.98)
		≥37	Reference
Second trimester	0.97 (0.91–1.02)	<32	1.00 (0.85–1.17)
		32–36	0.96 (0.91–1.02)
		≥37	Reference
Third trimester	1.09 (1.03–1.15)	<32	1.36 (1.16–1.59)
		32–36	1.05 (0.99–1.12)
		≥37	Reference

^a Odds ratios for 16.53 μg/m³ (averaged IQR) increase of PM₁₀ were calculated in each trimester, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

^b Gestational age of neonates

^c Odds ratios for 16.53 μg/m³ increase of PM₁₀ were calculated in each trimester by separate logistic regression analysis according to the gestational age of neonates, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

gestational age of the neonates. To accomplish this, separate logistic regression analyses were conducted according to the gestational ages of the preterm babies, which was subdivided into two sets (25–31 and 32–36 weeks). The results of these analyses showed that the risks for preterm delivery that was attributed to PM₁₀ exposures differed based on the gestational age of neonates, and that these risks were significantly higher for premature babies with relatively shorter gestational ages in the third trimester.

We also used multiple linear regression analysis to confirm that PM₁₀ exposure in the third trimester during pregnancy was a significant risk factor for preterm birth and obtained similar results to those obtained using the logistic regression method (Table 4). When we added an interactive effect between gestational age of the neonates and PM₁₀ exposure to the multiple regression model, we were able to verify that the risk for reduced gestational age as a result of PM₁₀ exposure was significant in each trimester during pregnancy, but was slightly higher in the third trimester than in the first or second trimester. In addition, the estimated regression coefficients of PM₁₀ exposure on gestational age were reduced in a dose-dependant manner as the gestational age of the neonates

decreased, and the risk for reduced gestational age associated with PM₁₀ exposures tended to be higher for preterm babies that were born earlier, regardless of the period of PM₁₀ exposure.

Because our data concerned the time-to-event data, we next performed Cox proportional hazards regression analysis after adjusting for confounding factors and a long-term trend effect, to estimate the hazard ratios for preterm birth according to 16.53 μg/m³ increase of PM₁₀ exposure level during each trimester (Table 5). Almost same hazards for preterm delivery that was attributed to PM₁₀ exposure were found in all trimesters, which were not statistically significant. It was hard to explain that there was not a risk for preterm birth associated with PM₁₀ exposure; however, it was biologically well-explained that there were varied effects for birth weight reduction by PM₁₀ exposure according to gestational age of the neonates. Therefore, we needed to use the methodology to estimate hazards varied with exposure period of the neonates in survival analysis. Moreover, the hazard ratios estimated by the Cox regression model were not valid statistically, since the assumption of proportional hazard function for PM₁₀ exposure during each trimester was violated ($P < 0.01$ for

Table 4 Regression parameter estimates for gestational age (weeks) according to PM₁₀ exposure in each trimester during pregnancy in a linear regression model

Period of PM ₁₀ exposure	Beta ^a (95% CI)	Gestational age (weeks) ^b	Beta ^c (95% CI)
First trimester	0.04 (0.03–0.06)	<32	–2.40 (–2.42 to –2.39)
		32–36	–1.02 (–1.03 to –1.01)
		37	–0.54 (–0.54 to –0.53)
		>37	0.08 (0.08–0.09)
Second trimester	0.02 (0.01–0.04)	<32	–2.40 (–2.42 to –2.39)
		32–36	–1.02 (–1.03 to –1.01)
		37	–0.54 (–0.54 to –0.53)
		>37	0.08 (0.07–0.09)
Third trimester	–0.05 (–0.06 to –0.04)	<32	–2.44 (–2.46 to –2.43)
		32–36	–1.06 (–1.07 to –1.05)
		37	–0.57 (–0.58 to –0.56)
		>37	0.04 (0.03–0.05)

^a Regression coefficients estimated for 16.53 µg/m³ (averaged IQR) increase of PM₁₀ were calculated in each trimester without taking time-dependent condition of PM₁₀ exposure into consideration, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

^b Gestational age of neonates

^c Regression coefficients estimated for 16.53 µg/m³ increase of PM₁₀ were calculated in each trimester after consideration of time-dependent condition of PM₁₀ exposure, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

Table 5 Hazard ratios for developing preterm delivery according to PM₁₀ exposure in each trimester during pregnancy

Period of PM ₁₀ exposure	Cox proportional hazards model	Test for nonproportionality		Gestational age (weeks) ^b	Extended Cox model with time-dependent exposure
	HR ^a (95% CI)	χ ² statistic (df)	P value		
First trimester	1.00 (0.99–1.01)	29.85 (1)	<0.0001	<32	1.23 (1.14–1.33)
				32–36	1.15 (1.09–1.21)
				37	1.07 (1.04–1.10)
				>37	1.00 (0.99–1.00)
Second trimester	1.00 (0.99–1.01)	7.66 (1)	0.006	<32	1.10 (1.03–1.18)
				32–36	1.07 (1.02–1.12)
				37	1.03 (1.01–1.06)
				>37	1.00 (0.99–1.01)
Third trimester	1.00 (0.99–1.01)	26.48 (1)	<0.0001	<32	1.21 (1.12–1.29)
				32–36	1.13 (1.08–1.19)
				37	1.07 (1.04–1.09)
				>37	1.00 (0.99–1.01)

^a Hazard ratios for 16.53 µg/m³ (averaged IQR) increase of PM₁₀ were calculated in each trimester without taking the time-dependent condition of PM₁₀ exposure into consideration, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

^b Gestational age of neonates

^c Hazard ratios for 16.53 µg/m³ increase of PM₁₀ were calculated in each trimester after consideration of the time-dependent condition of PM₁₀ exposure, after adjusting for gender of the infant, maternal age, paternal education, marital status, birth order, maternal occupation, maternal history of stillbirth, month and day of the week at birth, and a linear long-term trend effect

interactions of PM₁₀ exposure with time of exposure period). These results supported the finding that the hazard for preterm delivery associated with PM₁₀ exposure during each trimester changed according to the time of gestational

age of neonates. Therefore, we re-analyzed the data using an extended Cox model with time-dependent exposure after adjusting for confounding factors and a long-term trend effect and found that the estimated hazard ratio for

preterm birth to PM₁₀ exposure during each trimester varied with the gestational period of the neonates (Table 5). Among the periods of PM₁₀ exposure, the hazard ratios for preterm delivery associated with PM₁₀ exposure of the first and third trimester were slightly higher than those of the second trimester, and the trend of estimated hazard for preterm birth associated with PM₁₀ exposure increased in a dose-dependant way as gestational duration decreased. Additionally, the estimated hazard ratios for preterm birth attributable to PM₁₀ exposure were higher for preterm babies that were born within 25–31 weeks than for those that were born within 32–36 weeks, regardless of the PM₁₀ exposure period.

Discussion

Exposure to adverse environmental agents is a well-known cause of preterm delivery, and many studies have shown that exposure to air pollution, such as PM₁₀, leads to a greater risk of preterm delivery in each month or trimester during pregnancy. However, the period during pregnancy in which the effect of exposure is most significant has varied based on the location in which the study was conducted and the population used in the study. In a cohort study of 97,518 neonates in California, USA, Ritz et al. (2000) reported that the risk of preterm delivery after exposure to a 50 µg/m³ increase in PM₁₀ levels rose 13% during the first month of pregnancy and 18% during the 6th week before delivery using logistic regression analysis. Hansen et al. (2006) conducted a retrospective cohort study of 28,200 newborns in Brisbane, Australia, and found that the OR for preterm delivery attributed to a 4.5 µg/m³ increase in PM₁₀ exposure during the first trimester was 1.15 (95% CI = 1.06–1.25) using logistic regression analysis. In a study conducted on 52,113 neonates between 2001 and 2002 in Incheon, South Korea, Leem et al. (2006) found that the relative risk for preterm delivery was 1.27 times greater for women exposed to a high level of PM₁₀ exposure (64.6–106.4 µg/m³) than for those exposed to a low PM₁₀ (27.0–45.9 µg/m³) during the first trimester (95% CI = 1.04–1.56) using logistic regression analysis. In a previously conducted study of 382,100 newborn babies born in Seoul, South Korea, we detected a significant relationship between PM₁₀ concentrations during pregnancy and preterm birth by logistic regression, generalized additive logistic regression and the proportional hazard model with the risk of preterm delivery after a 42.5 µg/m³ increase in PM₁₀ exposure during the seventh month of pregnancy being 1.07 (95% CI = 1.01–1.14) when logistic regression model was used (Ha et al. 2004).

We used the extended Cox model with time-dependent PM₁₀ exposure to confirm that the estimated hazard ratio

for preterm birth to PM₁₀ exposure during each trimester varied with the gestational period of the neonates in this study. The results obtained using the extended Cox model with time-dependent exposure were similar to those obtained when the multiple regression model was used when the interaction of PM₁₀ exposure with gestational period was considered. The hazards for preterm birth associated with PM₁₀ exposure were higher with shorter gestational periods of neonates, and fetuses were affected more by PM₁₀ exposure with shorter gestational periods. This trend was consistent in each trimester; however, the hazard ratios for preterm delivery by PM₁₀ exposure in the first and third trimester were slightly higher than those in the second trimester. Therefore, the risks for preterm delivery or reduced gestational age attributable to PM₁₀ exposure during pregnancy according to the exposure period during pregnancy need to be further investigated. We note that the PM₁₀ effects on the births after 37 weeks of gestation, which were as considered as censored data in the Cox model, can be statistically interpreted as the effects of exposure duration. But the PM₁₀ effects on the births after 37 weeks of gestation are not meaningful as an epidemiological estimate of the preterm risk.

Survival analysis involves a statistical data analysis for which the outcome variable of concern is time until an event takes place. Preterm birth is characteristic of a time that corresponds to the gestational age until preterm birth occurs, therefore, it is reasonable to study preterm delivery using survival analysis. In O'Neill et al. (2003), they confirmed that survival analysis has an advantage over logistic regression analysis by accounting for time dependent exposure and outcome. They performed a sensitivity analysis to prove that the HR is better estimate than the OR in their study of urinary tract infection and preterm delivery (O'Neill et al. 2003). In this study, we used the extended Cox model after accounting for the time-dependent covariate to show that the effect of PM₁₀ exposure differs with gestational period, and we found that this time-to-event analysis is more effective than conventional approaches in the study of preterm delivery. Platt et al. (2004) verified the effectiveness of the use of the extended Cox model with time-varying covariates for the study of fetal and infant death. In this study, we found that the effect of PM₁₀ exposure on preterm delivery changes according to gestational period. Therefore, the environmental exposures that lead to an increased risk of preterm delivery in each trimester during pregnancy should be studied by different gestational periods.

It should be noted that our study had several limitations, including a lack of individual risk factors for preterm delivery, a low concentration of air pollutants in residential areas. We did not evaluate an accurate distance between each participant's home address and the closest monitoring

station due to a lack of exact Geographic Information System (GIS) data. Also, we could not take Caesarian section into account in the model, since the Birth data obtained from the Korea National Statistical Office had no information about a way of delivery. However, this study also showed several interesting features and strengths. For example, we found that PM₁₀ exposure had a greater impact on fetuses with a shorter gestational age, which is reasonable considering the immaturity of the defense mechanisms to toxic insults of exogenous chemicals; however, this has rarely been shown in other studies on preterm birth. Our study also included a larger sample of Korean women than other studies.

In conclusion, the risk for preterm birth attributable to PM₁₀ exposure differed by gestational periods. In studies evaluating the association of air pollution exposure during pregnancy to the risk for preterm delivery, exposure period during pregnancy should be considered.

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