Prenatal Exposure to PM_{10} and Preterm Birth between 1998 and 2000 in Seoul, Korea

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Objectives : The exposure to particulate air pollution during the pregnancy has reported to result in adverse pregnancy outcome such as low birth weight, preterm birth, still birth, and intrauterine growth retardation (IUGR). We aim to assess whether prenatal exposure of particulate matter less than 10 (m in diameter (PM_{10}) is associated with preterm birth in Seoul, South Korea.

Methods : We included 382,100 women who delivered a singleton at 25-42 weeks of gestation between 1998 and 2000. We calculated the average PM10 exposures for each trimester period and month of pregnancy, from the first to the ninth months, based on the birth date and gestational age. We used three different models to evaluate the effect of air pollution on preterm birth; the logistic regression model, the generalized additive logistic regression model, and the proportional hazard model.

Results : The monthly analysis using logistic regression model suggested that the risks of preterm birth increase with PM_{10} exposure between the sixth and ninth months of pregnancy and the highest risk was observed in the seventh month (adjusted odds ratio=1.07, 95% CI=1.01-1.14). We also found the similar results using generalized additive model. In the proportional hazard model, the adjusted odds ratio for preterm births due to PM_{10} exposure of third trimester was 1.04 (95% CI=0.96-1.13) and PM_{10} exposure between the seventh month and ninth months of pregnancy was associated with the preterm births.

Conclusions : We found that there were consistent results when we applied the three different models. These findings suggest that air pollution exposure during the third trimester pregnancy has an adverse effect on preterm birth in South Korea.

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Key Words: Air pollution, Preterm birth, PM_{10}(Particulate matter)

INTRODUCTION

Short-term exposure in particulate air pollution can increase daily mortality [1,2] and especially infant mortality [3-6]. In addition, the exposure to particulate air pollution during the pregnancy has been reported to result in adverse pregnancy outcome such as low birth weight [3,7-11], preterm birth [9,12-17], still birth [18,19], and intrauterine growth retardation (IUGR) [8,17]. Our previous studies [20,21] in South Korea reported significant relationships between airborne particle concentration during the first trimester of pregnancy and low birth weight, particularly, particulate matter less than 10 ㎛ in diameter (PM_{10}) in 4th month of pregnancy (RR=1.04, 95% CI=1.007-1.074). However, studies of association between particulate matter and adverse pregnancy outcome still need to be further evaluated.

Fetuses are thought to be a subgroup of the population who could be vulnerable to the effects of air pollutants [22]. Recent studies have suggested that weak associations with preterm birth (OR, <1.03) were found with a 10 $\mu g/m^3$ increase in PM_{10} during pregnancy [9,12-13]. Because small reduction in mean gestational duration could have a substantial health effect [23], it is important to establish the relationship between particulate exposure and preterm birth.

This preterm birth is one of major concerns because of its impact on infant mortality and long-term morbidity. In addition, the rate of preterm delivery still remains high in most

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countries [24-26]. For example, the rate of preterm births in African Americans in the United States is 17.4%. In Korea, nationwide data regarding preterm birth is not available now, while the data based on 64 university hospital showed 5.6% for the incidence of preterm birth [27].

Even though recent studies have shown that prenatal exposure to air pollution was associated with preterm births, it was not conclusive which exposure period to air pollution during the pregnancy contributes to preterm delivery. Xu et al. [12] examined the acute effects of air pollution on preterm birth and suggested that 100 $\mu g/m^3$ increase in total suspended particulates (TSP) reduced gestational age by .075 week and .042 week, respectively. Ritz et al. [13] also evaluated whether the air pollution exposure during the pregnancy affects the preterm delivery. They reported that preterm birth was associated with PM_{10} exposure during the first month of pregnancy and 6 weeks before birth. On the other hand, TSP exposure in the first trimester increased the prematurity in Czech study [9].

These studies for the impact of air pollution on birth outcomes have focused on the risk of the event. However, we are interested in the robustness of the results as well as the risk, because data analyses could be sensitive to statistical models.

In this study, we used three different statistical models and assessed whether prenatal exposure of PM_{10} is associated with preterm birth between 1998 and 2000 in Seoul, South Korea.

Table 1. Odds ratios of preterm birth according to study variables

Risk factors	Number (%) of all births	Number (%) of preterm	OR (95% CI)
Maternal age (years)			
<=19	2121 (0.6)	77 (3.6)	1.33 (1.05 -1.68)
20-24	44657 (11.6)	1233 (2.8)	1.00
25-29	212847 (55.4)	5951 (2.8)	1.01 (0.95-1.08)
30-34	101737 (26.5)	3686 (3.6)	1.32 (1.24-1.41)
>=35	23143 (5.33)	1305 (5.6)	2.10 (1.94-2.28)
Paternal age (years)			
<=19	516 (0.1)	27 (5.2)	1.88 (1.28-2.78)
20-24	9060 (2.4)	291 (3.2)	1.13 (1.00-1.28)
25-29	129416 (33.7)	3689 (2.9)	1.00
30-34	176086 (45.9)	5315 (3.0)	1.06 (1.02-1.11)
>= 35	68707 (17.9)	2890 (4.2)	1.50 (1.42-1.57)
Maternal education (years)			
0-6	2470 (0.6)	123 (5.0)	1.62 (1.35-1.95)
7-9	13327(3.5)	558 (4.2)	1.35 (1.24-1.48)
10-12	202430(52.7)	6365 (3.1)	1.01 (0.97-1.04)
>=13	165962 (43.2)	5195 (3.1)	1.00
Paternal education (years)	68707 (17.9)		
0-6	3463 (0.9)	166 (4.8)	1.58 (1.35-1.85)
7-9	13756 (3.6)	557 (4.1)	1.33 (1.21-1.45)
10-12	153510 (40.0)	4918 (3.2)	1.04 (1.00-1.08)
>=13	212727 (55.5)	6557 (3.1)	1.00
Marital status			
Married	381628 (99.2)	12104 (3.2)	1.00
Unmarried	2919 (0.8)	150 (5.1)	1.65 (1.40-1.95)
Maternal occupation			
Not employed	322345 (84.1)	10238 (3.2)	1.00
Employed	60929 (15.9)	1972 (3.2)	1.02 (0.97-1.07)
Parity			
1st	207998 (54.1)	6291 (3.0)	1.00
2nd	149669 (38.9)	4909 (3.3)	1.09 (1.05-1.13)
3rd	24875 (6.5)	954 (3.8)	1.28 (1.19-1.37)
4th	1779 (0.5)	87 (4.9)	1.65 (1.33-2.05)
5th+	225 (0.1)	14 (6.2)	2.13 (1.24-3.66)
Gender			
Female	184654 (48.0)	5351 (2.9)	1.0
Male	199932 (52.0)	6904 (3.5)	1.20 (1.16-1.24)
Previous pregnancy			
Stillbirth	2338 (0.6)	171 (7.3)	2.42 (2.07-2.83)
Livebirth	382206 (99.4)	12084 (3.2)	1.00
Season of birth			
Spring	100393 (26.1)	2825 (2.8)	1.00
Summer	88515 (23.0)	3064 (3.5)	1.24 (1.18-1.30)
Fall	94793 (24.6)	2980 (3.1)	1.12 (1.06-1.18)
Winter	100885 (26.2)	3386 (3.4)	1.20 (1.14-1.26)

Methods

A. Study area and population

We obtained birth data in Seoul between January 1, 1998 and December 31, 2000 from the Korean National Birth Register. These records included gestational age, parental age and educational level, maternal occupation, marital status, parity, date of birth, infant's gender and birth order. We excluded women who delivered multiple babies (n= 6,422) and who had pregnancy duration less than 25 weeks or more than 42 weeks (n=260). Additionally excluded were subjects who had missing values for study variables (n= 2,486). Finally, we included women numbering 382,100 who delivered a singleton at 25-44 weeks of gestation between 1998 and 2000. Preterm birth was defined as less than 37 weeks of completed gestation, and 12,255 women (3.2 percent) delivered preterm baby in this study.

B. Air pollution data and exposure assessment

We obtained the PM_{10} data from the Department of the Environment. The concentrations of PM_{10} were measured by β-ray absorption [28]. Exposure measurements during the study period were taken from 27 monitoring stations where the 24-hr average concentrations for particulate matter (PM_{10}) were obtained.

We calculated the average exposures for each trimester period and month of pregnancy, from the first to the ninth month, based on the birth dates and gestational age.

C. Statistical analyses

We used three different models to evaluate the effect of air pollution on preterm birth; the

Table 2. Descriptive statistics and correlation coefficients of air pollutants

Pollutant	Descriptive statistics					Correlation			
	Mean	SD	IQR	Min.	Max.	PM_{10}	CO	NO_2	O_3
SO_2 (ppb)	7.85	4.03	4.33	2.93	28.73	0.54	0.75	0.67	-0.23
PM_{10} ($\mu g/m^3$)	66.21	32.42	42.48	10.36	249.19		0.57	0.70	0.04
CO (100ppb)	10.77	4.12	5.42	3.71	27.94			0.75	-0.43
NO_2 (ppb)	32.65	10.82	16.18	10.22	66.54				-0.21
O_3 (ppb)	22.95	12.64	17.28	3.11	69.91				

*: SD: standard deviation, Min: minimum, IQR: interquartile range, Max: maximum

Table 3. Odds ratios for preterm delivery by interquartile range increase of PM10 exposure during the pregnancy

Exposure	Odds ratio (95% confidence interval)*		Odds ratio (95% confidence interval)†		Hazard ratio (95% confidence interval)‡	
	Unadjusted	Adjusted §	Unadjusted	Adjusted ‖	Unadjusted	Adjusted §
Trimester						
First	1.11(1.04,1.18)	0.93 (0.86,1.01)	1.11(1.04,1.18)	1.12 (1.04,1.22)	1.11(1.04,1.18)	0.93(0.85,1.01)
Second	1.02(0.96,1.09)	0.98 (0.90,1.07)	1.02(0.96,1.09)	0.99 (0.92,1.07)	1.02(0.96,1.09)	0.98(0.90,1.06)
Third	1.00(0.94,1.07)	1.06 (0.97,1.15)	1.00(0.94,1.07)	1.04 (0.97,1.11)	1.00(0.94,1.06)	1.06(0.97,1.15)
Month						
1	1.11 (1.06,1.17)	0.99(0.93,1.06)	1.11 (1.06,1.17)	1.14 (1.07,1.20)	1.11(1.06,1.17)	0.99(0.93,1.05)
2	1.11 (1.05,1.16)	0.99(0.93,1.05)	1.11 (1.05,1.16)	1.11 (1.04,1.17)	1.10(1.05,1.16)	0.98(0.93,1.04)
3	1.01 (0.96,1.06)	0.93(0.88,0.99)	1.01 (0.96,1.06)	0.94 (0.89,0.99)	1.01(0.96,1.06)	0.93(0.88,0.99)
4	0.96 (0.92,1.01)	0.92(0.86,0.97)	0.96 (0.92,1.01)	0.88 (0.83,0.93)	0.96(0.92,1.01)	0.92(0.86,0.97)
5	0.99 (0.94,1.04)	0.97(0.91,1.03)	0.99 (0.94,1.04)	0.94 (0.89,0.99)	0.99(0.94,1.04)	0.97(0.91,1.03)
6	1.04 (0.99,1.09)	1.01(0.96,1.07)	1.04 (0.99,1.09)	1.05 (1.00,1.11)	1.04(0.99,1.09)	1.01(0.95,1.07)
7	1.08 (1.03,1.13)	1.07(1.01,1.14)	1.08 (1.03,1.13)	1.17 (1.11,1.23)	1.08(1.03,1.13)	1.07(1.01,1.13)
8	1.03 (0.98,1.08)	1.03(0.97,1.10)	1.03 (0.98,1.08)	1.06 (1.01,1.12)	1.03(0.98,1.08)	1.03(0.96,1.09)
9	1.01 (0.95,1.07)	1.06(0.99,1.14)	1.01 (0.95,1.07)	1.03 (0.97,1.08)	1.01(0.95,1.07)	1.06(1.00,1.14)

Analyzed by logistic regression in SAS(*)
Generalized additive logistic regression in S-PLUS(†)
proportional hazard model in SAS(‡)
§ Adjusted for infant gender, infant order, maternal age, paternal age, marriage status, parity, live birth, maternal occupation, paternal education level and season
‖ Adjusted for infant gender, infant order, maternal age, paternal age, marriage status, parity, live birth, maternal occupation, paternal education level and date

logistic regression model, the generalized additive logistic regression model, and the proportional hazard model. All variables were selected by stepwise selection method.

1. Logistic regression model and Generalized additive logistic regression model

The logistic regression model analyzes data for binary outcome - the status of preterm. The second model, the generalized additive logistic regression model, also analyzes binary outcome, but the difference between two models is the method to control seasonal trend. To control seasonal effect for preterm occurrence, we used four indicator variables, spring, summer, fall, and winter with spring as the baseline in the logistic regression model. In the generalized additive model, we used the nonparametric smoothing function with LOESS (locally-weighted smoother) for the time variable to control long-term trends and seasonality. We chose the span equal to 0.2 that makes AIC smallest [29].

The odds ratio of preterm occurrence was estimated using the logistic regression and generalized additive model. The model formula for the two models is as follows.

Logistic regression model;

$\log\{p / 1\text{-}p\} = \beta_1 X_1 + \beta_2 X_2 +, \ldots, + \beta_p X_p$

GAM model; $\log\{p / 1\text{-}p\} = \beta_1 X_1 + \beta_2 X_2 +, \ldots, + S_p X_p$ (S=smoothing function)

2. Proportional hazard model

For the third statistical model, we applied the proportional hazard model, which is often used in survival data analysis, to analyze the hazards of preterm occurrence. We used the pregnancy period as a survival time and preterm birth as an event. Proportional hazard model is different from the above two models, and it arranges survival times in order. Hazard ratios are calculated in every ordered time, and overall hazard ratios of preterm occurrence were estimated. This model can be expressed as

$\log\{h(t) / h_0(t)\} = \beta_1 X_1 + \beta_2 X_2 +, \ldots, + \beta_p X_p$

h(t) is a hazard function of preterm and h0(t) is a baseline hazard function. A proportional hazard model assumes that different individuals have hazard functions that are proportional to one another [30].

3. Controlling of seasons and other covariates

We added time trend with LOESS smoother to the explanatory variables in the generalized additive model. Season of birth was also added in logistic regression as dummy variables. To evaluate the effect of air pollution considering possible confounders, we controlled several risk factors that could induce preterm births. Available risk factors in the Seoul birth certification data were infantile gender and order, parental age, marital status, parental occupation and educational level, and experience of previous stillbirth. Among these factors, we excluded paternal occupation and maternal education because these two factors did not affect preterm birth significantly.

We estimated the crude odds ratio and adjusted odds ratio (AOR) after controlling potential confounders and compared the results from the three models. In addition, we showed the graph of cumulative hazard of preterm occurrence between low and high PM_{10} exposed groups. The data were analyzed using the statistical package SAS, version 8.0 and S-Plus, version 4.0.

Results

The risks of preterm birth by study variables are shown in table 1. In the study subjects, mean gestational age was 39.4 weeks and the prevalence of preterm was 3.2%. The preterm was increased in those who were more than 35 years old, unmarried, and had experience of delivering stillbirth. The higher birth order was, the more preterm occurred. Parents who had educational experience less than 10 years were more likely to deliver preterm births. The

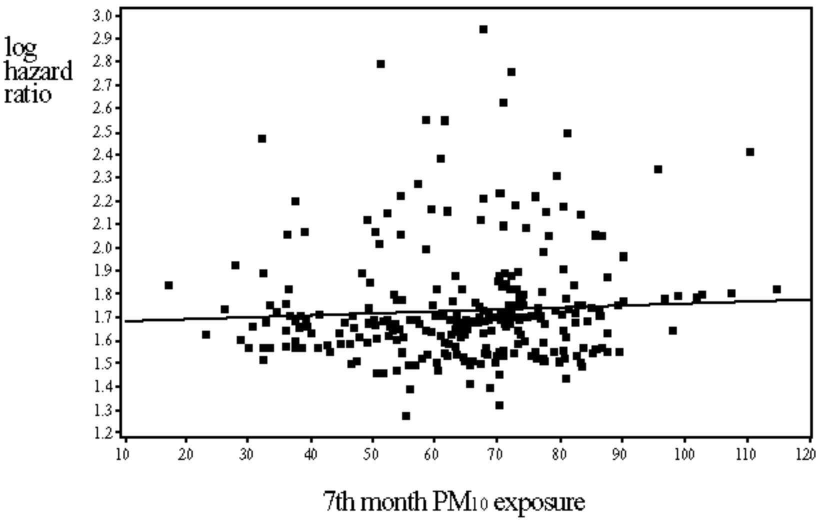
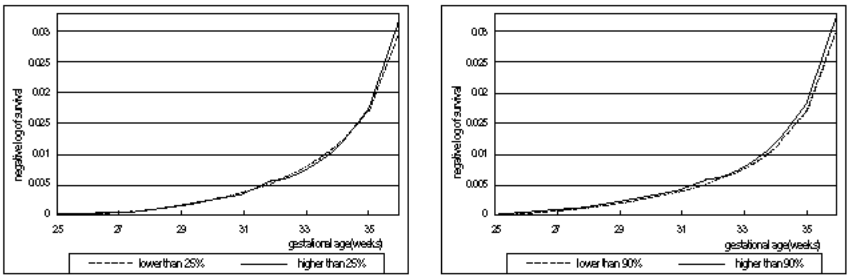


Figure1. Relationship between 7th month PM_{10} exposure and log of hazard ratio



(a) Divided on the basis of 25% value of PM_{10} (b) Divided on the basis of 90% value of PM_{10}

Figure2. Difference of cumulative hazard functions between low and high PM_{10} concentration groups during the seventh month of pregnancy.

prevalence of preterm births was significantly higher in mothers whose age was less than 19 years or more than 35 years compared with those of 20-24 years old. Unmarried mothers were more likely to deliver preterm infants than married mothers, and women who experienced stillbirth before showed increased risk of preterm births 2.42 times. The average level of PM_{10} from 1997 to 2000 was 66.7 $\mu g/m^3$ and interquartile range was 42.5 $\mu g/m^3$ (Table 2). The PM_{10} was positively correlated with SO_2, CO and NO_2 ($p<0.05$).

Table 3 shows, using logistic regression model, the crude odds ratios of preterm were 1.11 (95% CI=1.04-1.18), 1.02 (95% CI=0.96-1.09) and 1.00 (95% CI=0.94-1.06) for an interquartile range of PM_{10} in the first, second and third trimesters, respectively. In the analyses of monthly exposure during the pregnancy, we found that the risks for preterm tended to increase with PM_{10} exposure in the first month, second month, and also between the sixth and eighth months. We also found the similar results using generalized additive model and proportional hazard model. However, the effect size estimated by GAM was greatest among the three models.

Figure 1 shows the relationship between 7th month PM_{10} exposure and log of hazard ratio. We averaged log of hazard ratio per PM_{10} concentration, and predicted linear regression line. This graph shows a positive relationship in that the hazard of preterm occurrence increases with PM_{10} concentration.

We divided PM_{10} exposure into two groups for two ways i.e. by the levels of 25th and 90th percentile. We then compared cumulative hazard functions between the two groups. Figure 2 shows that group exposed to higher levels of PM_{10} concentration have a greater hazard than those in the lower concentration group. The difference of the risks for preterm births between two groups increased when we used the higher cut-off points.

DISCUSSION

We found that prenatal exposure to PM_{10} during mid to late pregnancy was associated with preterm birth. The highest risk of preterm birth for PM_{10} exposure was observed in 7th month (OR=1.07, 95% CI=1.01-1.14). Four studies have measured relationship between air pollution and preterm delivery. The three studies that assessed the effect of exposure to particulate matter, measured either as TSP or as PM_{10}, reported positive results for this association and two of them reported that exposures, late in pregnancy, to particulate matter increased the risk for preterm birth [31]. In a Chinese study using the time-series approach, exposure to total suspended particulates reduced the gestation of pregnancy and increased the occurrence of preterm delivery [12]. A study in Southern California considered the exposure in the first, and the second months of pregnancy as well as the 1st, 2nd, 4th, 6th, 8th and 26th weeks before birth [13]. It was reported that preterm birth was associated with exposure to PM_{10} in the first month of pregnancy and 6 weeks before birth. Bobak [9] found that prematurity increased with exposure to SO_2 and TSP during the first trimester after adjustment for gender, parity, maternal age, education, marital status, nationality and month of birth. Recently, Wilhelm and Ritz [14] reported that women living close to heavy traffic roadways are more likely to deliver the preterm birth because they are exposed to higher levels of motor vehicle exhaust, which released the compounds such as fine particles and carbon monoxide.

In this study, the hazard of preterm birth increased with PM_{10} concentration. Especially PM_{10} exposure during the third trimester was associated with preterm births after adjustment of infant gender and order, parental age, marital

Table 4. Air pollution and preterm birth in several published studies

Study period (Author)	Area	Air pollutant	Effect period	Effect size
1988 (Xu et al, 1995)*	Beijing	TSP, SO_2	7-d lagged moving average	Reduction of .075wk(12.6h) and .042wk(7.1h) for 100 ß /ß© increase in SO_2 and TSP
1989-1993 (Ritz et al., 2000) †	Southern California	PM_{10}	Averaging over 6 weeks before birth	A 20% increase in preterm birth for 50 $\mu g/m^3$ increase in PM10
		CO	First month of pregnancy 6 weeks before birth	A 16% increase for 50 $\mu g/m^3$ increase in PM_{10} A 13% increase only for the inland regions
1991 (Bobak, 2000) ‡	Czech	SO_2, TSP, NO_x	First trimester	1.27 (CI, 1.1-1.39) and 1.18 (CI, 1.05-1.31) for 50$\mu g/m^3$ increase in SO_2 and TSP
1994-1996 (Wilhelm and Ritz, 2003) §	LA County California	A distance weighted traffic density (DWTD)	Fall/Winter third trimester	1.15(95% CI 1.05-1.26)
1988-1999 (Woodruff et al., 2003) ‖	United States	Five criteria Pollutants (PM_{10}, O_3, CO, NO_2, SO_2)	-	Small increase of preterm delivery in a county with high air pollution
1986-1998 (Liu et al., 2003)¶	Canada	SO_2, NO_2, CO, O_3	Last month of pregnancy	SO_2 (OR=1.09, 95% CI, 1.01-1.19, for a 5.0ppb increase) CO (OR=1.08, 95% CI, 1.01-1.15, for a 1.0ppm increase)

* Acute Effects of Total Suspended Particles and Sulfur Dioxides on Preterm Delivery: A Community-Based Cohort Study
† Effect of Air Pollution on Preterm Birth Among Children Born in Southern California Between 1989 and 1993
‡ Outdoor air pollution, low birth weight, and prematurity
§ Residential Proximity to Traffic and Adverse Birth Outcomes in Los Angeles County, California, 1994-1996
‖ Disparities in Exposure to Air Pollution during Pregnancy
¶Association between Gaseous Ambient Air Pollution and Adverse Pregnancy Outcomes in Vancouver, Canada

status, live birth, maternal occupation, educational level of parent, and season by logistic regression as well as the GAM. In addition, we found that a group exposed to a higher concentration experience greater hazard than the lower concentration group using proportional hazard model.

These data suggest that exposure to particulate matter in pregnancy may adversely affect the gestation period. However, the biological mechanism regarding which toxicant associated with particulate matter could affect fetal growth remain to be explained

Several potential mechanisms for the biological effect could be considered.

Firstly, air pollution exposures during pregnancy may increase intrauterine infection [32]. For example, PM_{10} exposure may increase maternal susceptibility to infections during the weeks before birth. Secondly, the potential mechanisms could be related to hematological factors. There are reports of increased blood viscosity and plasma fibrinogen related to coagulation during air pollution and these hematological factors may influence the blood perfusion of the placenta and placental functions [33-35]. Thirdly, air pollution may affect DNA directly producing placental DNA adducts that has been reported to be higher among mothers exposed to higher levels of air pollution [36].

There are several limitations in this study. First, we did not control several potential confounders that is known to have an impact on preterm delivery, e.g., weight gain during pregnancy, cervical and vaginal infection, vaginal bleeding and chronic disease such as hypertension, diabetes, and asthma. Second, there is exposure misclassification due to the fact that we only used data from a fixed air monitoring station instead of personal air sampling. However, because these factors are not expected to be correlated with daily air pollution levels [37], the estimated effects of air pollution are unlikely to be confounded by them.

However, our study shows considerable strengths. We used and compared the three models for analysis by monthly, and as far as we know it is the first time to use survival function in the air pollution study. In preterm birth analysis, gestational age less than 37 weeks were event and the others were censored. Because preterm birth was defined by the gestational age less than 37 weeks, we can determine event or censored status depending on the survival time. Therefore, we concluded that the application of the proportional hazard model was appropriate to evaluate the effect of air pollution on preterm birth.

In summary, we had consistent results when we applied the three different models. These findings suggest that air pollution exposure during the third trimester pregnancy has an adverse effect on preterm birth in South Korea.

Therefore, we should try to understand factors contributing to these observed developmental and reproductive effects. These efforts will provide valid data for risk assessment, which contribute to the promotion of better education and understanding in regards to the reproductive health of women and healthier children.

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