

# Exposure to air pollution during different gestational phases contributes to risks of low birth weight

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**BACKGROUND:** Although there have been growing concerns about the adverse effects of air pollution on birth outcomes, little is known about which specific exposure times of specific pollutants contribute to low birth weight (LBW). **METHODS:** We evaluated the relationships between LBW and air pollution exposure levels in Seoul, Korea. Using the air pollution data, we estimated the exposure during each trimester and also during each month of pregnancy on the basis of the gestational age and birth date of each newborn. Generalized additive logistic regression analyses were conducted considering infant sex, birth order, maternal age, parental education level, time trend, and gestational age. **RESULTS:** The monthly analyses suggested that the risks for LBW tended to increase with carbon monoxide (CO) exposure between months 2–5 of pregnancy, with exposure to particles <10 µm (PM<sub>10</sub>) in months 2 and 4, and for sulphur dioxide (SO<sub>2</sub>) and nitrogen dioxide (NO<sub>2</sub>) exposure between months 3–5. **CONCLUSIONS:** This study suggests that exposure to CO, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> during early to mid pregnancy contribute to risks for LBW.

*Key words:* air pollution/carbon monoxide/low birth weight/PM<sub>10</sub>/nitrogen dioxide/sulphur dioxide

## Introduction

Low birth weight (LBW) increases not only infant mortality (Bobak and Leon, 1992; Woodruff *et al.*, 1997; Loomis *et al.*, 1999) but also the subsequent morbidity (Lin *et al.*, 1999; Gouveia and Fletcher, 2000; Hack *et al.*, 2002). The rates of LBW reach up to 50% in some developing countries (CDC, 2002), although they range from 5.0–7.9% in developed countries (Ventura *et al.*, 1998).

In recent years, air pollution is considered to be an important cause or risk factor for reproductive health. There have been growing concerns about the adverse effects of air pollution on birth outcomes such as LBW, intrauterine growth retardation (IUGR), preterm births and birth defects (Bobak and Leon, 1992; Dejmek *et al.*, 1999; Bobak, 2000; Ritz *et al.*, 2002). A lot of evidence for the effect of air pollution on LBW has been published, although there are many other risk factors such as infant sex and race, paternal weight and height, gestational weight gain, parity, caloric intake, maternal morbidity during pregnancy, cigarette smoking and alcohol consumption (Kramer, 1987). Studies conducted in China, the Czech Republic, and the United States reported a relationship between air pollution and LBW (Wang *et al.*, 1997; Bobak, 2000; Maisonet *et al.*, 2001). The results of these studies, however, are not consistent, particularly regarding the effect period of each air pollutant.

Some studies reported that exposure during the first trimester was associated with an increased risk for LBW. In an animal study, the period shortly after conception was the most susceptible to the induction of developmental changes by air pollutants (Generoso *et al.*, 1987; Rutledge, 1997). Human studies also suggested that initial changes leading to IUGR might be triggered in early pregnancy, around the time of implantation (Khong *et al.*, 1986; Duvekot *et al.*, 1995). A number of epidemiological studies indicated that the risk for LBW or IUGR is also increased in the first trimester of pregnancy. Dejmek *et al.* (1999) found the risk of IUGR associated with exposure to particles <10 µm in aerodynamic diameter (PM<sub>10</sub>) during the first month of pregnancy. Bobak (2000) also reported that air pollutants [sulphur dioxide (SO<sub>2</sub>) and total suspended particulate] had greater effects on LBW in the first trimester than other trimesters.

On the contrary, other studies have suggested that exposure to air pollution during the last trimester has greater effects on LBW. Gruenwald (1978) showed that the peak period for weight growth is around 33 weeks gestation. In terms of air pollution, third trimester exposure to total suspended particles (TSP) and SO<sub>2</sub> was associated with increased risk of LBW in Beijing (Wang *et al.*, 1997). In addition, carbon monoxide (CO) exposure during the third trimester was associated with LBW in Southern California (Ritz and Yu, 1999) and the North-Eastern United States (Maisonet *et al.*, 2001).

These inconsistencies raise the issue of whether the peak effect period of air pollution on LBW differs across different populations and pollutants. Furthermore, previous studies investigated the relationship between air pollution and LBW using a broad range of exposure times. Thus, little is known about which specific exposure time of specific pollutants contributes to LBW. Therefore, we evaluated the specific timing of peak effects of air pollutants on LBW throughout the gestational period.

## Materials and methods

In South Korea, birth certificate records were based on records compiled by doctors or nurses at delivery and registered with regional public health centres. These data included birth weight, sex, birth order, gestational age, maternal age, parental educational level and parental occupation. The gestational age was usually estimated based on maternal report for last menstrual period (LMP) and on ultrasound measurements by gynaecologists. We collected birth data in Seoul between January 1, 1996 and December 31, 1998 from the Korean National Birth Register. We excluded missing data ( $n = 3642$ ) for any co-variables and preterm births ( $n = 13\,835$ ) which were defined as <37 weeks gestation (Wang *et al.*, 1997; Ritz and Yu, 1999). The study subjects were restricted to mothers who delivered full-term singletons between 37 and 44 gestational weeks during the study period ( $n = 388\,105$ ). LBW was defined as <2500 g.

We obtained air pollution data from the Department of the Environment regarding concentrations of PM<sub>10</sub> (by  $\beta$ -ray absorption), SO<sub>2</sub> (by ultraviolet fluorescence), CO (by non-dispersive infrared photometry) and nitrogen dioxide (NO<sub>2</sub>) by chemiluminescence between January 1, 1995 and December 31, 1998 in Seoul (Ministry of Environment and National Institute of Environmental Research, 1999). Exposure measurements during the study period were taken from 20 monitoring stations covering nearly all areas of the city. The major source of air pollution in the study area is automobile exhaust emissions. We averaged the hourly measurements arithmetically across all monitoring stations and calculated a 24 h average. These data were used to estimate the exposure during each trimester and each month of pregnancy on the basis of the gestational age and birth date of each newborn.

We used a generalized additive model (GAM), which allowed regressions to include non-parametric smooth functions in order to control the potential non-linear dependence of each birth on date and season (Hastie and Tibshirani, 1996). First, we included a smoothing function for date and/or season in the model using LOESS, a moving regression smoother to control for seasonal and long-term trends (Cleveland and Devlin, 1988). The model fitted well when the date only was entered into the model. The selection criterion for goodness of fit was evaluated using Akaike's information criterion (AIC) (Akaike, 1973). We similarly chose the number of degrees of freedom for gestational age that lowered the AIC. Second, we controlled the co-variables, which are known as risk factors for LBW. We applied the model both with and without parental occupation, and obtained the better-fitted model for this analysis without parental occupation. Finally, the optimal model included indicator variables for infant sex, birth order, maternal age, parental education level, time trend and gestational age.

We calculated average concentrations for each pollutant through the whole period, in each trimester (1st, 2nd and 3rd) and in each month of pregnancy. The gestational period was divided into three trimesters of ~3 calendar months (Cunningham *et al.*, 2001). The air pollution data were analysed as both continuous and categorical variables. We

categorized pollutant levels into quartiles. To assess an exposure-response relationship, we applied the models in which dummy variables were used to indicate categories based on quartiles of the pollutant concentrations. Exposure in the bottom quartile for each pollutant was used as the reference category. We present the risk magnitudes as odds ratios (OR) of LBW associated with the interquartile change of each pollutant. In order to clarify the specific effect period of air pollution exposure on LBW, we created two separate subgroups based on exposure levels during pregnancy and analysed the two separately. To assess the effect of exposure during the latter 5 months of pregnancy, we formed subgroup 1, which included only mothers who were at low exposure levels (<25th of each air pollutant level) during the first 5 months of pregnancy. To assess the effect of exposure during the first 5 months of pregnancy, we restricted subgroup 2 to those who were at low exposure levels during the latter 5 months of pregnancy.

## Results

Table I presents the demographic characteristics of infants delivered in Seoul from January 1, 1996 to December 31, 1998. The prevalence of LBW was 2.9% of singletons, but 4.6% when preterm births were included. The OR for LBW increased for female sex, fourth or higher order child, mothers <20 years of age and parents with low educational level.

Table II lists the concentrations of air pollutants during the study period. Mean levels were 1.2 ppm (1.4  $\mu\text{g}/\text{m}^3$ ) for CO, 71.1  $\mu\text{g}/\text{m}^3$  for PM<sub>10</sub>, 12.1 ppb (47.5  $\mu\text{g}/\text{m}^3$ ) for SO<sub>2</sub> and 32.5 ppb (61.1  $\mu\text{g}/\text{m}^3$ ) for NO<sub>2</sub>. No air pollutant exceeded the WHO recommended criteria.

The correlations among the pollutants of each trimester are in Table III. The concentrations of CO, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> were positively correlated with each other.

The risks of LBW for exposure to air pollution during whole pregnancy and each trimester are presented in Table IV. Regarding the whole period of pregnancy exposures, all of the

**Table I.** Demographic characteristics of infants delivered between 1996 and 1998 in Seoul

Variables	Mean birth weight	% of low birth weight	OR (95% CI) <sup>a</sup>
Sex of the infant			
Male	3357.3	1.2	1
Female	3250.0	1.7	1.61 (1.55–1.68)
Infant birth order			
First	3291.0	3.0	1
Second	3314.1	2.7	0.77 (0.74–0.80)
Third	3368.2	3.3	0.92 (0.85–0.99)
Fourth +	3346.3	5.9	1.65 (1.36–2.00)
Maternal age (years)			
20 +	3248.2	2.9	1
<20	3306.0	4.5	1.77 (1.47–2.13)
Maternal education			
University	3300.4	2.7	1
High school	3309.0	3.0	1.19 (1.14–1.24)
Middle school	3301.3	3.8	1.56 (1.45–1.68)
Paternal education			
University	3296.7	2.7	1
High school	3306.5	3.1	1.23 (1.18–1.28)
Middle school	3305.9	3.9	1.58 (1.47–1.70)

<sup>a</sup>Adjusted date and gestational age; OR = odds ratio for LBW; CI = confidence interval.

pollutants exhibited hazardous effects on LBW. In terms of trimester-specific exposures, we found that first-trimester CO exposure increased the risk for LBW (OR = 1.04, 95% CI = 1.01–1.07), as did second-trimester exposure to PM<sub>10</sub> (OR = 1.04, 95% CI = 1.00–1.08), SO<sub>2</sub> (OR = 1.06, 95% CI = 1.02–1.11), and NO<sub>2</sub> (OR = 1.03, 95% CI = 1.01–1.06). On the other hand, these effects disappeared in the third trimester. In addition, interquartile changes of CO during the first trimester decreased birth weight by 12.8 g. Furthermore, reduction of birth weight was 19.6, 14.6 and 21.5 g for interquartile increase of PM<sub>10</sub>, SO<sub>2</sub>, and NO<sub>2</sub> respectively, in the second trimester (data not shown). Figure 1 shows the OR of LBW for each quartile of CO, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> during each trimester of pregnancy. The risks of LBW were increased in infants with first-trimester CO exposure in the 25–50th percentiles (RR = 1.011, 95% CI = 0.958–1.066), in the 50–75th percentiles (RR = 1.012, 95% CI = 0.957–1.069), and ≥75th percentile (RR = 1.060, 95% CI = 1.006–1.117). We found positive dose response relationships between LBW and CO during the first trimester, and between LBW and PM<sub>10</sub>, SO<sub>2</sub> during the second

trimester. Higher CO, PM<sub>10</sub> and SO<sub>2</sub> levels showed higher risks of LBW.

When the exposure for each month of pregnancy was evaluated separately, the resulting OR for LBW are shown in Figure 2. We found that the risks for LBW tended to increase with CO exposure between months 2–5, and with PM<sub>10</sub> exposure between months 2–4 compared with the latter 5 months. For SO<sub>2</sub> and NO<sub>2</sub>, exposure between the months 3–5 of pregnancy was associated with LBW. These findings suggest that air pollutants affect LBW in the earlier periods of pregnancy.

Table V compares the OR changes of LBW between the periods of pregnancy before and after the 5th month. When mothers were exposed to low concentrations of PM<sub>10</sub> and CO during the first 5 months of pregnancy, the association between LBW and air pollution was not significant regardless of exposure in the latter period of pregnancy. On the other hand, exposure during the first 5 months of pregnancy was consistently associated with LBW even if the air pollution levels were low during the latter 5 months of pregnancy. This separate analysis suggests again that air pollution exposure during the earlier months of pregnancy is more important in the relationship between air pollutant and LBW.

**Table II.** Descriptive statistics for air pollution, Seoul, 1995–1998

Pollutants	Mean (SD)	Min	Q1	Med	Q3	Max
CO (ppm)	1.2 (0.5)	0.4	0.9	1.1	1.4	3.4
PM <sub>10</sub> (µg/m <sup>3</sup> )	71.1 (30.1)	18.4	47.4	67.6	89.3	236.9
SO <sub>2</sub> (ppb)	12.1 (7.4)	3.0	6.8	9.8	15.6	46.0
NO <sub>2</sub> (ppb)	32.5 (10.2)	10.2	25.0	31.4	39.7	65.1

SD = standard deviation; Min = minimum; Q1 = lower quartile; Med = median; Q3 = upper quartile; Max = maximum.

**Table III.** Pearson correlation coefficients between air pollutants in pregnancy trimesters

	CO	PM <sub>10</sub>	SO <sub>2</sub>
First trimester			
PM <sub>10</sub>	0.47		
SO <sub>2</sub>	0.79	0.78	
NO <sub>2</sub>	0.77	0.66	0.75
Second trimester			
PM <sub>10</sub>	0.68		
SO <sub>2</sub>	0.86	0.82	
NO <sub>2</sub>	0.78	0.81	0.77
Third trimester			
PM <sub>10</sub>	0.69		
SO <sub>2</sub>	0.86	0.85	
NO <sub>2</sub>	0.82	0.80	0.76

**Discussion**

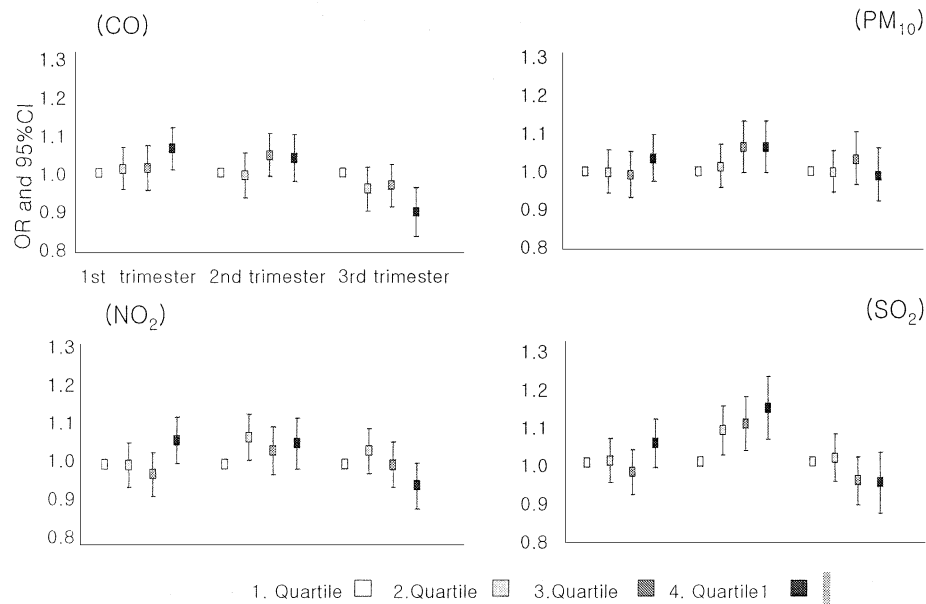
Research in several countries has shown that air pollution affects LBW (Table VI). Our previous study indicated that ambient CO, NO<sub>2</sub>, SO<sub>2</sub>, and TSP concentrations during the first trimester of pregnancy were associated with LBW (Ha et al., 2001). In the current study, we extended the study period from 1996–1997 to 1996–1998 and focused more specifically on exposure during pregnancy. This study suggested that exposure to air pollution during the first and second trimester was associated with an increased risk for LBW. More specifically, we found that the risks for LBW increased with CO exposure between months 2–5, and with SO<sub>2</sub> and NO<sub>2</sub> exposure between months 3–5 of pregnancy. PM<sub>10</sub> exposure in the second and fourth months was associated with LBW.

We found that exposure during the third trimester was negatively associated with LBW. Wang et al. (1997) suggested that it might be due to the pattern of air pollution whereby the concentration of air pollutants during the first and second trimesters is almost inversely associated with that of the third trimester. We cannot explain it fully and further study is needed.

**Table IV.** Odds ratios and their 95% confidence intervals of LBW for interquartile range increases of air pollutants during pregnancy<sup>a</sup>

	First trimester	Second trimester	Third trimester	All trimesters
CO	1.04 (1.01–1.07)	1.03 (1.00–1.06)	0.96 (0.93–0.99)	1.05 (1.01–1.09)
PM <sub>10</sub>	1.03 (1.00–1.07)	1.04 (1.00–1.08)	1.00 (0.95,1.04)	1.06 (1.01–1.10)
SO <sub>2</sub>	1.02 (0.99–1.06)	1.06 (1.02–1.11)	0.96 (0.91–1.00)	1.14 (1.04–1.24)
NO <sub>2</sub>	1.02 (0.99–1.04)	1.03 (1.01–1.06)	0.98 (0.96–1.00)	1.04 (1.00–1.08)

<sup>a</sup>Adjusted for date, gestational age, infant sex, infant order, maternal age and parental education level.



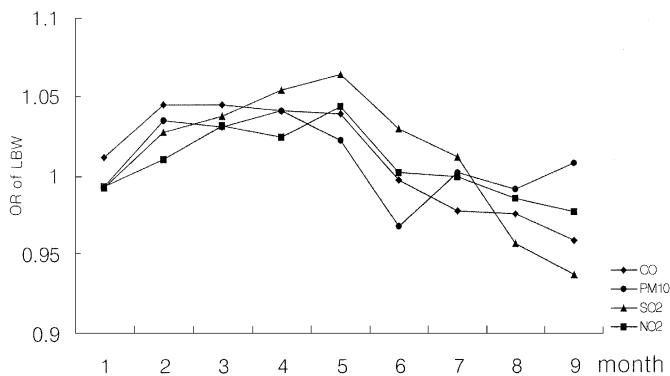
**Figure 1.** Odds ratio and 95% confidence interval for low birth weight by quartiles of air pollutants in trimesters of pregnancy from logistic regression models adjusted for all covariates.

**Table V.** Odds ratios and their 95% confidence intervals for LBW with exposure before and after the 5th month of pregnancy

Subgroup	Exposure	Odds ratios (95% confidence interval)	
		PM <sub>10</sub>	CO
Subgroup 1 <sup>a</sup>	Last 5 months	0.94 (0.85–1.05)	0.88 (0.79–0.99)
Subgroup 2 <sup>b</sup>	First 5 months	1.04 (1.01–1.08)	1.06 (0.98–1.14)

<sup>a</sup>Only mothers who were at low exposure levels during the first 5 months of pregnancy were included. Odds ratios were calculated based on the interquartile range of air pollution levels during the last 5 months of pregnancy.

<sup>b</sup>Only mothers who were at low exposure levels during the last 5 months of pregnancy were included. Odds ratios were calculated based on the interquartile range of air pollution levels during the first 5 months of pregnancy.



**Figure 2.** Odds ratio of low birth weight for interquartile range change of air pollutants in each month of pregnancy.

The biological mechanisms whereby air pollution might influence birth weight remain to be explained. One hypothesized pathway is that placental inflammation may play an important role in the physiological pathway between air pollution exposure and LBW. It is possible that air pollution during pregnancy leads to placental inflammation, which impairs placental function (Dexter *et al.*, 2000). Salafia *et al.*

(1995) reported that chronic inflammation brought about growth restriction, independently of placental vasculopathy. In the present study, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> exposures from first through second trimesters appeared to have the largest effect on LBW. In terms of the biological mechanism on LBW, it is reasonable to consider PM<sub>10</sub>, SO<sub>2</sub>, and NO<sub>2</sub> together rather than separately because they represent fine particles that are believed to be a risk pollutant (Ha *et al.*, 2001). In addition, these pollutants were correlated strongly with each other and exerted an effect on LBW within similar periods. Particle exposure *in vitro* and in exposed animals causes oxidative stress (Carter *et al.*, 1997; Kadiiska *et al.*, 1997) and can increase the permeability of lung epithelium (Li *et al.*, 1994), allowing particles access to the endothelial cells and the blood (Donaldson *et al.*, 2001). PM<sub>10</sub> and gaseous pollutants such as SO<sub>2</sub> and NO<sub>2</sub> lead to pulmonary inflammation with a systemic release of cytokines (Walters *et al.*, 2001; Nemmar *et al.*, 2002) and increase blood viscosity (Peters *et al.*, 1997; Prescott *et al.*, 2000). Increased blood viscosity is associated with decreased oxygen diffusion (Zondervan *et al.*, 1988) and may interfere with the supply of oxygen and nutrients to the fetus. In addition, some toxicants from air pollutants could cross the

**Table VI.** Air pollution and low birth weight in several published studies

Study period	Area	Air pollutant	Effect period	Effect size
Early 1970s (Williams <i>et al.</i> , 1977)	California LA	CO	–	Decrease 314 g of mean birth weight in heavily polluted areas
1988–1994 (Wang <i>et al.</i> , 1997)	Beijing	SO <sub>2</sub> , TSP	Third trimester	100 µg/m <sup>3</sup> increase SO <sub>2</sub> 1.11 (1.06–1.16) TSP 1.10 (1.05–1.14)
1989–1993 (Ritz and Yu, 1999)	LA	CO	Third trimester	CO > 5.5 ppm 1.22 (1.03–1.44)
1994–1996a (Dejmek <i>et al.</i> , 1999)	Teplice	PM <sub>10</sub>	First month	PM <sub>10</sub> low (reference group) Medium 1.62 (1.07–2.50) High 2.64 (1.48–4.71)
1991 (Bobak, 2000)	Czech	TSP, SO <sub>2</sub>	First trimester	50 µg/m <sup>3</sup> increase TSP 1.20 (1.11–1.30) SO <sub>2</sub> 1.15 (1.07–1.24)
1994–1996 (Maisonet <i>et al.</i> , 2001)	Northeastern United States	CO, SO <sub>2</sub>	Third trimester Second trimester	CO 1 ppm increase 1.31 (1.06–1.62) SO <sub>2</sub> 25th centile (reference group) 25–<50th centile 1.21 (1.07–1.37) 50–<75th centile 1.20 (1.08–1.35) 75–<95th centile 1.21 (1.03–1.43)

<sup>a</sup>Study for the effect of air pollution on IUGR.

CO = carbon monoxide; SO<sub>2</sub> = sulphur dioxide; TSP = total suspended particles; PM<sub>10</sub> = particles <10 µm.

placenta with direct effects on fetal development (Dejmek *et al.*, 1999).

Alternatively, placental insufficiency may be an important pathway. Placental insufficiency reduces the oxygen and nourishment supplies to the fetus (Behrman, 1992) and leads to growth retardation (Cunningham *et al.*, 2001a,b). Exposure to air pollution in early pregnancy could cause insufficient trophoblast formation, and lead to insufficient placental vascularization (Roberts *et al.*, 1991; Duvokot *et al.*, 1995). Chronic reductions of uteroplacental circulation due to the effects of air pollution could result in fetal hypoxia and IUGR (Wilson, 1971; Werler *et al.*, 1985).

A number of potential mechanisms for CO have been suggested. The fetus in the uterus may be particularly susceptible to hypoxia from CO exposure even if the maternal blood level of CO is non-toxic (Gabielli *et al.*, 1995). Therefore, exposure to low levels of ambient CO during pregnancy could result in tissue hypoxia by increasing maternal and fetal carboxyhaemoglobin concentrations and decreasing fetal O<sub>2</sub> tensions or O<sub>2</sub> carrying capacity (Longo, 1976). Furthermore, maternal CO inhalation can affect the fetus more severely than the mother in terms of oxygenation of tissues (Longo, 1977).

This study has several limitations. We did not consider several potential risk factors for LBW, including parental weight and height, history of adverse pregnancy outcomes, maternal nutrition, gestational weight gain, cigarette smoking, alcohol consumption and occupational exposures (Paige and Davis, 1986; Kramer, 1987; Teitelman *et al.*, 1990; Dejmek *et al.*, 2002). However, because these factors are not expected to be correlated with daily air pollution levels (Schwartz and Morris, 1995), the estimated effects of air pollution are unlikely to be confounded by these factors. On the other hand, when two pollutants were evaluated together, the effects of CO on LBW in the first trimester remained significant. In the second trimester, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> were associated with LBW after controlling for CO. However, it is difficult to interpret this result because of co-linearity among pollutants (Pitard and Viel, 1997). In addition, we used data from an ambient air monitoring station in exposure assessment and this may have

resulted in exposure misclassification. However, recent studies have suggested that outdoor monitors can be used as surrogates for personal exposure (Janssen *et al.*, 1998, 1999). Even if there is a measurement error, it would not much bias the estimates and used to underestimate the effect of air pollution (Schwartz and Levin, 1999; Zeger *et al.*, 2000).

On the other hand, our study had several strengths. We examined various specific exposure periods for air pollutants during pregnancy. Although Dejmek and Ritz analysed air pollution on the basis of average monthly exposure for IUGR and birth defects respectively (Dejmek *et al.*, 1999; Ritz *et al.*, 2002), ours is the first study, to our knowledge, to identify an association between LBW and monthly exposure during pregnancy. We suggest that exposure to CO, PM<sub>10</sub>, SO<sub>2</sub> and NO<sub>2</sub> during early to mid pregnancy contribute to risks for LBW. Elucidating the biological mechanism for the effect of specific air pollutants on LBW will certainly be a task for future study.

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### References

- Akaike, H. (1973) Information theory and an extension of the maximum likelihood principal. In Petrov, B.N. and Csaki, F. (eds) *2nd International Symposium on Information Theory*. Akademiai Kiado. Budapest. 267–281.
- Berhman, R.E. (1992) *Nelson Textbook of Pediatrics*. 14th edn. WB Saunders, Philadelphia, USA.
- Bobak, M. and Leon, D.A. (1992) Air pollution and infant mortality in the Czech Republic, 1986–88. *Lancet*, **340**, 1010–1014.
- Bobak, M. (2000) Outdoor air pollution, low birth weight, and prematurity. *Environ. Health. Perspect.*, **108**, 173–176.
- Carter, J.D., Ghio, A.J., Samet, J.M. and Devlin, R.B. (1997) Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. *Toxicol. Appl. Pharmacol.*, **146**, 180–188.
- CDC (2002) Youth and Family: Low Birth Weight Babies. Available [http://hnb.ffh.vic.gov.au/commcare/yafs\\_yf.nsf/](http://hnb.ffh.vic.gov.au/commcare/yafs_yf.nsf/) [accessed 3 March 2002].
- Cleveland, W.S. and Delvin, S.J. (1988) Robust locally-weighted regression and smoothing scatterplots. *J. Am. Stat. Assoc.*, **74**, 829–836.
- Cunningham, F.G., Gant, N.F., Levend, K.J., Gilstrap, L.C 3rd., Hauth, J.C.

- and Wenstrom, K.D. (2001a) *Williams Obstetrics 21st* edn. McGraw-Hill Companies, New York, USA. p 130.
- Cunningham, F.G., Gant, N.F., Levend, K.J., Gilstrap, L.C 3rd., Hauth, J.C. and Wenstrom, K.D. (2001b) *Williams Obstetrics 21st* edn. McGraw-Hill Companies, New York, USA. pp 745–746.
- Dejmek, J., Selevan, S.G., Ivan Benes, I., Solansky, I. and Šrám, R.J. (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. *Environ. Health Perspect.*, **107**, 475–480.
- Dejmek, J., Solansky, I., Podrazilova, K. and Sram, R.J. (2002) The exposure of non-smoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. *Environ. Health Perspect.*, **110**, 601–606.
- Dexter, S.C., Pinar, H., Malee, M.P., Hogan, J., Carpenter, M.W. and Vohr, B.R. (2000) Outcome of very low birth weight infants with histopathologic chorioamnionitis. *Obstet. Gynecol.*, **96**, 172–177.
- Donaldson, K., Stone, V., Seaton, A. and MacNee, W. (2001) Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environ. Health Perspect.*, **109**, 523–527.
- Duvekot, J.J., Cheriex, E.C. and Pieters, F.A.A. (1995) Severely impaired growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. *Acta. Obstet. Gynecol. Scand.*, **74**, 693–697.
- Ministry of Environment and National Institute of Environmental Research (1999) Annual Report of Ambient Air Quality in Korea, 1998. Ministry of Environment, Gwacheon, South Korea.
- Gabrielli, A., Layon, A.J. and Gallarher, T.J. (1995) Carbon monoxide intoxication during pregnancy: A case presentation and pathophysiologic discussion, with emphasis on molecular mechanisms. *J. Clin. Anesth.*, **7**, 82–87.
- Generoso, W.M., Rutledge, J.C., Cain, K.T., Hughes, L.A. and Braden, P.W. (1987) Exposure of female mice to ethylene oxide within hours after mating leads to fetal malformation and death. *Mutat. Res.*, **176**, 269–274.
- Gouveia, N. and Fletcher, T. (2000) Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. *Occup. Environ. Med.*, **57**, 477–483.
- Gruenwald, P. (1978) Intrauterine growth. In Stave, V. (ed) *Perinatal physiology*. Plenum Press, New York, NY, USA. pp 1–18.
- Ha, E.H., Hong, Y.C., Lee, B.E., Woo, B.H., Schwartz, J. and Christiani, D.C. (2001) Is air pollution a risk factor for low birth weight in Seoul? *Epidemiology*, **12**, 643–648.
- Hack, M., Flannery, D.J., Schluchter, M., Cartar, L., Borawski, E. and Klein, N. (2002) Outcomes in young adulthood for very-low-birth-weight infants. *N. Engl. J. Med.*, **346**, 149–157.
- Hastie, T.J. and Tibshirani, R.J. (1996) *Generalized additive models*. Chapman & Hall, London, UK.
- Janssen, N.A., Hoek, G., Brunekreef, B., Harssema, H., Mensink, I. and Zuidhof, A. (1998) Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am. J. Epidemiol.*, **147**, 537–547.
- Janssen, N.A., Hoek, G., Harssema, H. and Brunekreef, B. (1999) Personal exposure to fine particles in children correlates closely with ambient fine particles. *Arch. Environ. Health*, **54**, 95–100.
- Kadiiska, M.B., Mason, R.P., Dreher, K.L., Costa, D.L. and Ghio, A.J. (1997) In vivo evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. *Chem. Res. Toxicol.*, **10**, 1104–1108.
- Khong, T.Y., De Wolf, F., Robertson, W.B. and Brosens, I. (1986) Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br. J. Obstet. Gynaecol.*, **93**, 1049–1059.
- Kramer, M.S. (1987) Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization*, **65**, 663–737.
- Li, X.Y., Donaldson, K., Rahman, I. and MacNee, W. (1994) An investigation of the role of glutathione in increased epithelial permeability induced by cigarette smoke in vivo and in vitro. *Am. J. Respir. Crit. Care Med.*, **149**, 1518–1525.
- Lin, C.A., Martins, M.A., Farhat, S.C., Pope, C.A., 3rd, Conceicao, G.M., Anastacio, V.M., Hatanaka, M., Andrade, W.C., Hamaue, W.R., Bohm, G.M. et al. 1999. Air pollution and respiratory illness of children in Sao Paulo, Brazil. *Paediatr. Perinat. Epidemiol.*, **13**, 475–488.
- Longo, L.D. (1976) Carbon monoxide: effects on oxygenation of the fetus in utero. *Science*, **194**, 523–525.
- Longo, L.D. (1977) The biological effects of carbon monoxide on the pregnant women, fetus, and newborn infant. *Am. J. Obstet. Gynecol.*, **129**, 69–103.
- Loomis, D., Castillejos, M., Gold, D.R., McDonnell, W. and Borja-Aburto, V.H. (1999) Air pollution and infant mortality in Mexico City. *Epidemiology*, **10**, 118–123.
- Maisonet, M., Bush, T.J., Correa, A. and Jaakkola, J.J.K. (2001) Relation between ambient air pollution and low birth weight in the Northeastern United States. *Environmen. Health Perspect.*, **109** (Suppl), S351–S356.
- Nemmar, A., Hoet, P.H.M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbilloen, H., Mortelmans, L., Nemery, B. et al. (2002) Passage of inhaled particles into the blood circulation in humans. *Circulation*, **105**, 411–414.
- Paige, D. and Davis, L.R. (1986) Fetal growth, maternal nutrition, and dietary supplementation. *Clin. Nutr.*, **5**, 191–199.
- Peters, A., Doring, A., Wichmann, H.E. and Koenig, W. (1997) Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet*, **349**, 1582–1587.
- Pitard, A. and Viel, J.F. (1997) Some methods to address co-linearity among pollutants in epidemiological time series. *Stat. Med.*, **16**, 527–544.
- Prescott, G.J., Lee, R.J., Cohen, G.R., Elton, R.A., Lee, A.J., Fowkes, F.G. and Agius R.M. (2000) Investigation of factors which might indicate susceptibility to particulate air pollution. *Occup. Environ. Med.*, **57**, 53–57.
- Ritz, B. and Yu, F. (1999) The effect of ambient carbon monoxide on low birth weight among children born in Southern California between 1989 and 1993. *Environ. Health Perspect.*, **107**, 17–25.
- Ritz, B., Yu, F., Fruin, S., Chapa, G., Shaw, G.M. and Harris, J.A. (2002) Ambient air pollution and risk of birth defects in Southern California. *Am. J. Epidemiol.*, **155**, 17–25.
- Roberts, J.M., Taylor, R.N. and Goldfein, A. (1991) Clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. *Am. J. Hypertens.*, **4**, 700–708.
- Rutledge, J.C. (1997) Developmental toxicity induced during early stages of mammalian embryogenesis. *Mutat. Res.*, **396**, 113–127.
- Salafia, C.M., Ernst, L.M., Pezzullo, J.C., Wolf, E.J. and Rosenkrantz, T.S. (1995) The very low birth weight infant: maternal complications leading to preterm birth, placental lesions, and intrauterine growth. *Am. J. Perinatol.*, **12**, 106–110.
- Schwartz, J., Morris, R. (1995) Air pollution and hospital admission for cardiovascular disease in Detroit, Michigan. *Am. J. Epidemiol.*, **142**, 23–35.
- Schwartz, J. and Levin, R. (1999) Drinking water turbidity and health. *Epidemiology*, **10**, 86–90.
- Teitelman, A.M., Welch, L.S., Hellenbrand, K.G. and Btacken, M.B. (1990) Effect of maternal work activity on preterm birth and low birth weight. *Am. J. Epidemiol.*, **131**, 104–113.
- Ventura, S.J., Martin, J.A., Curtin, S.C. and Mathews, T.J. (1998) Report of final natality statistics, 1996. Monthly vital statistics report. vol 46, no. 11 (Suppl). National Center for Health Statistics, Hyattsville, Maryland, USA.
- Walters, D.M., Breyse, P.N. and Wills-Karp, M. (2001) Ambient urban Baltimore particulate-induced airway hyperresponsiveness and inflammation in mice. *Am. J. Respir. Crit. Care Med.*, **164**, 1438–1443.
- Wang, X., Ding, H., Ryan, L. and Xu, X. (1997) Association between air pollution and low birth weight: a community-based study. *Environ. Health Perspect.*, **105**, 514–520.
- Werler, M.M., Pober, B.R. and Holmes, L.B. (1985) Smoking and pregnancy. *Teratology*, **32**, 473–481.
- Williams, L., Spence, A. and Tideman, S.C. (1977) Implications of the observed effects of air pollution on birth weight. *Soc. Biol.*, **24**, 1–9.
- Wilson, E.W. (1971) The effect of smoking in pregnancy on the placental coefficient. *N.Z. Med. J.*, **74**, 384–385.
- Woodruff, T.J., Grillo, J. and Schoendorf, K.C. (1997) The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. *Environ. Health Persp.*, **105**, 608–612.
- Zeger, S.L., Thomas, D., Dominici, F., Samet, J.M., Schwartz, J., Dochery, D. and Cohen, A. (2000) Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ. Health Perspect.*, **108**, 419–426.
- Zondervan, H.A. Oosting, J., Smorenberg-Schoorl, M.E. and Treffers, P.E. (1988) Maternal whole blood viscosity in pregnancy hypertension. *Gynecol. Obstet. Invest.*, **25**, 83–88.

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