# Association between Gaseous Ambient Air Pollutants and Adverse Pregnancy Outcomes in Vancouver, Canada

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**The association between ambient air pollution and adverse health effects, such as emergency room visits, hospitalizations, and mortality from respiratory and cardiovascular diseases, has been studied extensively in many countries, including Canada. Recently, studies conducted in China, the Czech Republic, and the United States have related ambient air pollution to adverse pregnancy outcomes. In this study, we examined association between preterm birth, low birth weight, and intrauterine growth retardation (IUGR) among singleton live births and ambient concentrations of sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), carbon monoxide (CO), and ozone in Vancouver, Canada, for 1985–1998. Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for such effects. Low birth weight was associated with exposure to $SO_2$ during the first month of pregnancy (OR = 1.11, 95% CI, 1.01–1.22, for a 5.0 ppb increase). Preterm birth was associated with exposure to $SO_2$ (OR = 1.09, 95% CI, 1.01–1.19, for a 5.0 ppb increase) and to CO (OR = 1.08, 95% CI, 1.01–1.15, for a 1.0 ppm increase) during the last month of pregnancy. IUGR was associated with exposure to $SO_2$ (OR = 1.07, 95% CI, 1.01–1.13, for a 5.0 ppb increase), to $NO_2$ (OR = 1.05, 95% CI, 1.01–1.10, for a 10.0 ppb increase), and to CO (OR = 1.06, 95% CI, 1.01–1.10, for a 1.0 ppm increase) during the first month of pregnancy. In conclusion, relatively low concentrations of gaseous air pollutants are associated with adverse effects on birth outcomes in populations experiencing diverse air pollution profiles. *Key words:* air pollution, intrauterine growth retardation, low birth weight, preterm birth, risk assessment, sulfur dioxide. *Environ Health Perspect* 111:1773–1778 (2003). doi:10.1289/ehp.6251 available via *http://dx.doi.org/* [Online 4 August 2003]**

Over the last 20 years, numerous studies in Canada and elsewhere have confirmed a positive relation between air pollution and morbidity and mortality (Burnett et al. 1997a, 1997b; Pope et al. 2002; Samet et al. 2000; Schwartz 1994). Findings from animal studies have provided evidence of an association between air pollution and reproductive and developmental anomalies (Bignzmi et al. 1994; Falkner 1986; Kavlock et al. 1979, 1980). Until recently, however, few epidemiologic studies have examined the potential effects of ambient air pollution on birth outcomes (Bobak 1999, 2000; Bobak and Leon 1999; Dejmek et al. 1999; Dolk et al. 2000; Ritz and Yu 1999; Ritz et al. 2000; Rogers et al. 2000; Sram et al. 1996; Wang et al. 1997; Woodruff et al. 1997; Xu et al. 1995).

Birth weight, gestational age, and fetal growth are important indicators of perinatal health. Low birth weight (LBW), preterm birth, or intrauterine growth retardation (IUGR) are strongly associated with infant mortality and morbidity. The etiology of these adverse birth outcomes is complex but not yet well understood. In 1995, Xu et al. (1995) investigated the association between maternal exposure to air pollution during pregnancy and preterm delivery in a prospective cohort in four urban districts in Beijing, China. They found a significant reduction in the duration of gestation with increasing levels of sulfur dioxide and total suspended particulate (TSP). Wang et al. (1997) reported a significant negative association between maternal exposure to $SO_2$ and TSP during the third trimester of pregnancy and infant birth weight. These results indicate that TSP and $SO_2$, or a more complex mixture of these and other pollutants, may contribute to an elevated risk of LBW in the Beijing population. Results from similar studies in the United States, the Czech Republic, Great Britain, and Brazil have subsequently been reported (Bobak 1999, 2000; Bobak and Leon 1999; Dejmek et al. 1999; Dolk et al. 2000; Ritz and Yu 1999; Ritz et al. 2000; Rogers et al. 2000; Wang et al. 1997; Woodruff et al. 1997).

A study in the Czech Republic (Bobak 1999) found that TSP, $SO_2$, and nitrogen oxides were all associated with LBW among newborns. However, when the effects of all pollutants were assessed simultaneously in a multivariate statistical model, only $SO_2$ demonstrated a significant association with LBW. In Los Angeles, California (USA), exposure to higher levels of ambient carbon monoxide (CO; > 5.5 ppm averaged over 3 months) during the last trimester was associated with a significantly increased risk of LBW, after adjustment for potential confounders (Ritz and Yu 1999). In a study in Georgia (USA), exposures to environmental $SO_2$ and TSP were associated with an increased risk of very LBW (Rogers et al. 2000). However, no association between LBW and $SO_2$ was found in a study in Great Britain (Dolk et al. 2000).

In Canada, there have been several studies of the association between ambient air pollution and adverse health outcomes over the last decade (Burnett et al. 1997a, 1997b, 1998, 2000; Goldberg et al. 2001). These studies have found positive and statistically significant associations between the ozone–$SO_2$ pollution mix and hospital admissions for asthma, chronic obstructive pulmonary disease, and infections (Burnett et al. 1998) and between individual air pollutants and hospitalization for respiratory diseases (Burnett et al. 1997a) and hospital admissions for congestive heart failure in the elderly (Burnett et al. 1997b). Both gaseous and particulate pollutants have also been associated with increased mortality rates (Burnett et al. 2000). A more recent investigation also reported a positive association between tropospheric $O_3$ and cause-specific mortality, including deaths from cancer, cardiovascular diseases, and respiratory diseases in Montreal, Québec (Goldberg et al. 2001). However, no report has yet addressed associations between ambient air pollution and birth outcomes in Canada. In this study we examine this issue using data from a major Canadian city:Vancouver, British Columbia.

## Methods

***Air pollution exposure data.*** Continuous sampling measures for air pollutants have been compiled for the following 13 census subdivisions in the great Vancouver area: 15004, 15011, 15015, 15018, 15022, 15025, 15029, 15034, 15038, 15039, 15043, 15051, and 15803 (Statistics Canada 1997). These data contain daily average and daily 1-hr concentrations of the gaseous pollutants $SO_2$, nitrogen dioxide, CO, and $O_3$ for the period 1 April 1985 through 31 December 1998, and of ambient particulate matter with aerodynamic diameters ≤ 10 µm ($PM_{10}$) for the

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period 1 January 1994 through 31 December 1998. The arithmetic means and selected percentiles of the distribution of these gaseous pollutants are presented in Table 1, both for daily average concentrations and for daily 1-hr maximum concentrations.

Gaseous pollutant data were averaged across the available monitoring stations hour by hour. Daily averages (24 hr) were then computed from these hourly measurements. Any day with less than 22 of 24 possible hours of available information was considered missing. Because multisite hourly averages were computed even if measurements were available from only one site (a very rare occurrence), 24-hr average daily pollutant concentrations were available for the entire period covered by this study. We estimated missing pollutant data (< 1% of the total number of daily observations) using linear interpolation methods so that daily pollutant data were available throughout the 13-year period of interest.

***Live birth cohort.*** All live births were obtained from the live birth database maintained by Statistics Canada (Fair and Cyr 1993) for the period 1 January 1986 through 31 December 1998. The quality of these data has been previously validated for national perinatal surveillance system and research projects (Fair and Cyr 1993). The information in the database has been derived from birth certificates and includes date of birth, birth weight, gestational age, parity, birth order, maternal and paternal age, and residence. Gestational age is determined by the responsible obstetrician, based on all available information, including date of last menstrual period and the mother's estimate of the date of conception, and in recent years increasingly including ultrasound dating. Previous research suggests that gestational age information in the database is reliable (Kramer et al. 2000). Maternal residence during pregnancy is recorded at the provincial census subdivision. Individual data of all singleton live births for the 13 census subdivisions in the Vancouver area noted above were abstracted from the database and used in the present study.

***Linkage of the two databases.*** Environmental air pollution data were available at the census subdivision level. Exposure levels from conception through delivery were determined by linkage with this environmental database, which includes daily average concentrations of the gaseous pollutants of interest. Dates on the air pollution records were matched temporally to the date of birth and length of gestation. For each live birth, therefore, average air pollution concentrations were retrospectively calculated for the first, second, and third month; the last and the next to last month of pregnancy; or for the first, second, or third trimester. For preterm birth and LBW, the maternal exposure window was expressed in months, because preterm or LBW births may involve only 6–8 months of gestation. For IUGR births, the exposure window was expressed in both months and trimesters.

Maternal exposures in each month or trimester of pregnancy were calculated for ambient $SO_2$, $NO_2$, CO, and $O_3$. These were estimated by the arithmetic means of all daily measurements by all monitors in the residential area of each mother. There were no changes in the placement of the monitoring stations or the monitoring instruments during the study period.

A preterm birth is defined as a live birth with < 37 complete weeks of gestation. An LBW infant is defined as a live-birth infant weighing < 2,500 grams at birth. Live-birth infants with birth weights < 500 g or gestational ages < 22 weeks were excluded from all analyses. An IUGR birth is defined as an infant whose birth weight falls below the 10th percentile, by sex and gestational week, of all singleton live births in Canada between 1986 and 1998 (Health Canada 2000). In examining this indicator of pregnancy outcome, we included only live births at 37–42 weeks of gestation (i.e., full-term births).

***Statistical analysis.*** The fundamental hypothesis in this study is that temporal variation in ambient air pollution levels is associated with temporal variation in pregnancy outcomes. Adverse pregnancy outcomes, including preterm birth, LBW, and IUGR, defined as dichotomous categories, represent dependent variables in the analysis. Daily average concentrations of ambient $SO_2$, $NO_2$, CO, and $O_3$ represent independent variables. We examined the association between individual-level dependent variables and independent variables by multiple logistic regression. Initial analyses focused on the effects of a single pollutant; we then assessed the robustness of these effects using multiple pollutant models. Odds ratios (ORs) and 95% confidence intervals (CIs) for adverse pregnancy outcomes in relation to exposure to ambient air pollutants were calculated after controlling for maternal age (< 20, 20–24, 25–29, 30–34 and ≥ 35 years), parity, infant sex, gestational age or birth weight, and month of birth.

## Results

The concentrations of all pollutants varied appreciably, both for daily average and for daily 1-hr maximum concentrations (Table 1).

**Table 1.** Mean and selective percentiles of gaseous air pollutants: Vancouver, Canada, 1985–1998.

| | | Percentile | | | | | |
|---|---|---|---|---|---|---|---|
| Pollutant (unit) | Mean | 5th | 25th | 50th | 75th | 95th | 100th |
| $SO_2$ (ppb) | | | | | | | |
| Daily average | 4.9 | 1.5 | 2.8 | 4.3 | 6.3 | 10.5 | 30.5 |
| Maximum[a] | 13.4 | 4.3 | 7.8 | 11.7 | 16.8 | 28.3 | 128.5 |
| $NO_2$ (ppb) | | | | | | | |
| Daily average | 19.4 | 11.5 | 15.1 | 18.1 | 22.3 | 31.9 | 70.0 |
| Maximum[a] | 34.1 | 21.0 | 26.7 | 31.4 | 38.3 | 56.2 | 124.5 |
| CO (ppm) | | | | | | | |
| Daily average | 1.0 | 0.5 | 0.7 | 0.8 | 1.2 | 2.2 | 5.6 |
| Maximum[a] | 2.2 | 0.8 | 1.2 | 1.8 | 2.7 | 5.1 | 12.8 |
| $O_3$ (ppb) | | | | | | | |
| Daily average | 13.4 | 3.2 | 8.2 | 13.1 | 18.2 | 25.1 | 41.3 |
| Maximum[a] | 27.9 | 9.7 | 19.8 | 27.6 | 35.1 | 47.2 | 105.5 |

[a]Maximum 1-hr concentrations within a day.

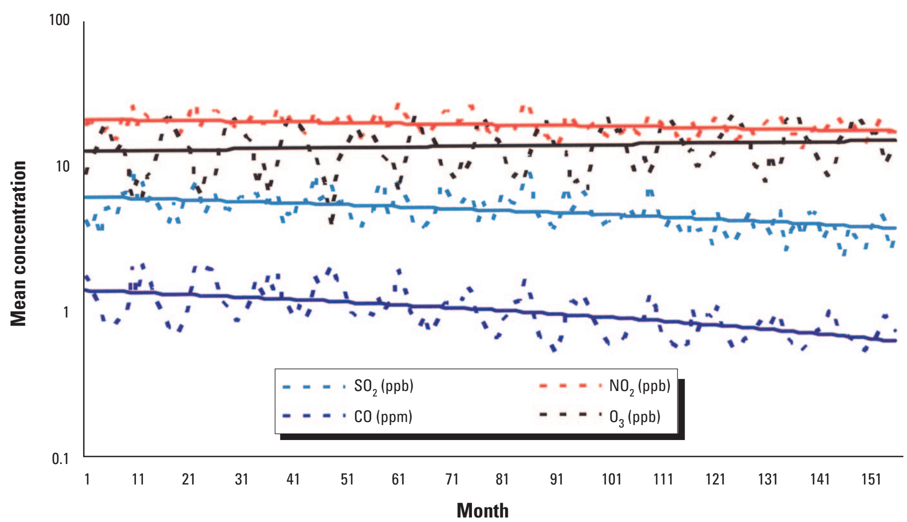


**Figure 1.** Variations in mean concentrations of air pollutants in Vancouver, by month, 1985–1998.

For example, the mean daily concentration of $SO_2$ was 4.9 ppb, with the 5th and 95th percentiles being 1.5 ppb and 10.5 ppb, respectively. The mean concentrations of all four pollutants are shown in Figure 1. All pollutants exhibit a clear seasonal variation. In addition, there were steady declines in the average concentrations of $SO_2$, $NO_2$, and CO, whereas $O_3$ showed a slight increase over time.

There were 229,085 singleton live births in the Vancouver study area between 1986 and 1998. The average LBW, preterm birth, and IUGR rates were 4.0, 5.3, and 9.4%, respectively. These rates varied by season of birth, infant sex, parity, maternal age, and time period of birth. IUGR rates among nonparous and younger (< 25 years) women were much higher (Table 2).

LBW and preterm birth rates appeared to be increasing slightly over the study period. Although IUGR rates show considerable variation as with LBW and preterm birth, a secular trend in IUGR does not appear in the data because that proportion of infants with IUGR is calculated relative to the national fetal growth curve during the same period (Figure 2).

Correlations among these pollutants are given in Table 3. Strong positive correlations were observed among $SO_2$, $NO_2$, and CO, with coefficients ranging from 0.61 to 0.72 ($p < 0.0001$). However, $O_3$ was inversely correlated with other pollutants, with coefficients of –0.35, –0.25, and –0.49 ($p < 0.0001$) for $SO_2$, $NO_2$ and CO, respectively.

Crude and adjusted ORs for LBW and preterm birth in relation to exposure to gaseous air pollution are given in Tables 4 and 5, respectively, for the first and last months of pregnancy. Overall, there were only slight differences between the crude and adjusted estimates of risk. Statistically significant increased adjusted ORs were observed for LBW and maternal exposure to $SO_2$ during first month of pregnancy (OR = 1.11, 95% CI, 1.01–1.22, for a 5.0 ppb increase), for preterm birth and $SO_2$ (OR = 1.09, 95% CI, 1.01–1.19, for a 5.0 ppb increase) or CO exposure (OR = 1.08, 95% CI, 1.01–1.15, for a 1.0 ppm increase) during the last month of pregnancy.

As shown in Table 6, increased risk of IUGR was observed to be caused by maternal exposure to three gaseous pollutants during the first month of pregnancy (OR = 1.07, 95% CI, 1.01–1.13, for a 5.0 ppb increase of $SO_2$; OR = 1.05, 95% CI, 1.01–1.10, for a 10.0 ppb increase of $NO_2$; OR = 1.06, 95% CI, 1.01–1.10, for a 1.0 ppm increase of CO). No significant elevation in risk was observed with $O_3$. Using pregnancy trimester to characterize the maternal exposure time window, IUGR is associated with exposure to $SO_2$ (OR = 1.07, 95% CI, 1.00–1.14, for a 5.0 ppb increase) and exposure to CO (OR = 1.05, 95% CI, 1.00–1.10, for a 1.0 ppm increase) during the first trimester of pregnancy, and exposure to $O_3$ (OR = 1.08, 95% CI, 1.01–1.15 for a 10.0 ppb increase) during the second trimester of pregnancy (Table 7).

To examine the robustness of adjustment for exposure to copollutants, we fit logistic regression models including each of the other pollutants individually, and then including all three additional gaseous pollutants simultaneously. The increased risk of LBW associated with exposure to $SO_2$ during the first month of pregnancy (OR = 1.11, 95% CI, 1.01–1.22) persisted after adjustment for $NO_2$ (OR = 1.22, 95% CI, 1.09–1.39), CO (OR = 1.23, 95% CI, 1.07–1.42), or $O_3$ (OR = 1.16, 95% CI, 1.04–1.28), as well as after adjustment for $NO_2$, CO, and $O_3$ simultaneously (OR = 1.29, 95% CI, 1.12–1.50).

Similarly, the elevated risks for preterm birth associated with $SO_2$ (OR = 1.09, 95% CI, 1.01–1.20) and CO (OR = 1.08, 95% CI, 1.00–1.20) during the last month of pregnancy remained elevated after adjustment for other gaseous copollutants, although not all adjusted risk estimates remained statistically significant. Elevated risks for IUGR associated with $SO_2$, $NO_2$, and CO during the first month of pregnancy also tended to persist after adjustment for copollutant exposure. This robustness was also observed for the association between IUGR and exposure to $SO_2$ and CO during the first trimester of pregnancy.

## Discussion

In our study, LBW was associated with maternal exposure to $SO_2$ during the first month of

**Table 2.** LBW (< 2,500 g), preterm birth (< 37 weeks' gestation), and IUGR among singleton live births, Vancouver, Canada, 1986–1998.

| Characteristics | No. of live births | LBW (%) | Preterm birth (%) | IUGR[a] |
|---|---|---|---|---|
| Total | 229,085 (100%) | 4.0 | 5.3 | 9.4 |
| Season of birth | | | | |
| Spring | 59,168 (25.8) | 3.9 | 5.2 | 9.2 |
| Summer | 58,942 (25.7) | 3.9 | 5.0 | 9.6 |
| Autumn | 56,695 (24.8) | 3.9 | 5.2 | 9.4 |
| Winter | 54,280 (23.7) | 4.3 | 5.8 | 9.5 |
| Male | 118,072 (51.5) | 3.8 | 5.8 | 9.6 |
| Parity | | | | |
| 0 | 108,419 (47.3) | 4.7 | 5.7 | 11.8 |
| 1 | 80,215 (35.0) | 3.3 | 4.7 | 7.4 |
| ≥ 2 | 40,451 (17.7) | 3.6 | 5.2 | 7.0 |
| Maternal age (years) | | | | |
| < 20 | 7,507 (3.3) | 5.5 | 6.7 | 11.9 |
| 20–24 | 36,592 (16.0) | 4.4 | 5.2 | 11.9 |
| 25–29 | 77,650 (33.9) | 3.8 | 4.9 | 9.5 |
| 30–34 | 73,387 (32.0) | 3.7 | 5.0 | 7.9 |
| ≥ 35 | 33,949 (14.8) | 4.5 | 6.4 | 8.1 |
| Period of birth | | | | |
| 1986–1989 | 63,953 (27.9) | 3.8 | 5.1 | 9.5 |
| 1990–1992 | 52,718 (23.0) | 4.0 | 5.4 | 9.4 |
| 1993–1995 | 56,912 (24.8) | 4.1 | 5.4 | 9.6 |
| 1996–1998 | 55,502 (24.2) | 4.1 | 5.4 | 9.2 |

[a]There are a total of 216,988 births after excluding all those with gestational age < 37 weeks.

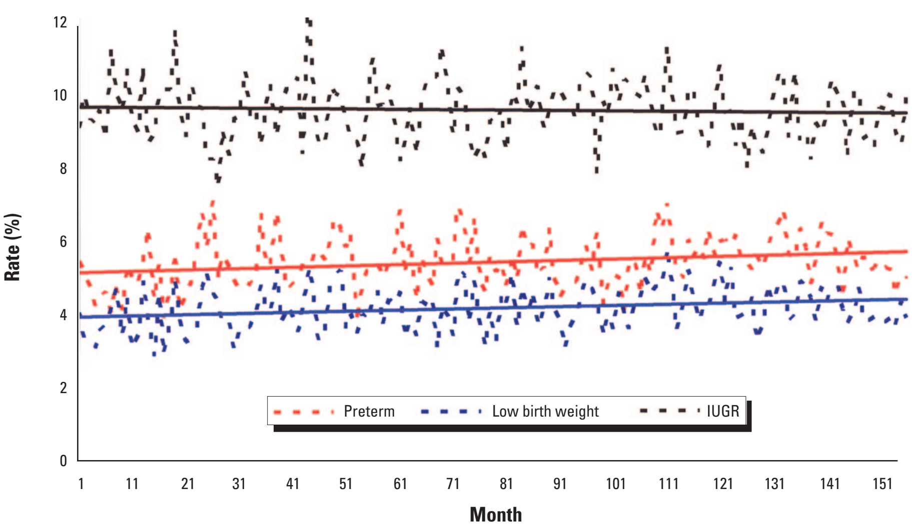


**Figure 2.** Temporal trends in LBW, preterm birth, and IUGR by month in Vancouver, 1986–1998.

pregnancy, and preterm birth was associated with $SO_2$ and CO during the last month. Fetal growth retardation was consistently associated with maternal exposure to $SO_2$, $NO_2$, and CO in the first month of pregnancy. The positive association between fetal growth retardation and exposure to gaseous air pollution persisted when maternal exposure was evaluated during the first trimester of pregnancy but was slightly weaker.

These results are generally consistent with the findings from China, the United States, and the Czech Republic. Our estimates of the effects of gaseous air pollution on birth weight and gestational age categorized as dichotomous variables are comparable with those found in the studies from China (Wang et al. 1997; Xu et al. 1995). These associations were not attenuated by adjustment for potential confounding factors, including season of birth. There are some differences between the results from the studies reported to date, however. In one Chinese study (Wang et al. 1997), LBW was associated with $SO_2$ and TSP in the last trimester of pregnancy, with ORs of 1.11 (95% CI, 1.06–1.16) and 1.10 (95% CI, 1.05–1.14) for a 100 μg/m$^3$ increase in $SO_2$ and TSP. However, exposures in earlier trimesters were not associated with birth outcomes. In a Czech study (Bobak 2000), IUGR was not associated with any of the pollutants measured, although the effects on LBW and preterm birth were statistically significant for exposures to $SO_2$ in the first trimester.

The present study is one of only a few studies using a large sample to assess the potential effects of maternal exposures to ambient air pollutants during pregnancy on birth weight, preterm birth, and IUGR. Our study has several strengths. First, this community-based investigation is less likely to suffer selection bias, healthy worker effects, or attribution than are occupationally based studies. Second, British Columbia birth registration is generally considered complete and reliable, with individual information on both mothers and infants recorded on birth certificates, including data on birth weight and gestational age. These data are recorded by a single, well-developed vital statistics registry and have been verified to be accurate for perinatal research purposes (Fair and Cyr 1993). Third, reliable measurements of daily $SO_2$, $NO_2$, CO, and $O_3$ concentrations obtained independently, from air monitoring stations, have previously been used in studies of the association between air pollution and morbidity (Burnett et al. 1997a, 1997b) and mortality (Burnett et al. 1998, 2000; Goldberg et al. 2001; Villeneuve et al. In press). Finally, the present analysis enjoys the strength of the time-series approach while offsetting limitations inherent in many previous time-series studies—notably, the lack of individual information on potential confounding or modifying factors and reliable information on the size of the population from which the cases were derived.

Although no information on socioeconomic status was available at the individual level, it is unlikely that socioeconomic status is an important confounder in this study for the following reasons. First, there is no evidence that socioeconomic factors are associated with air pollution in the Vancouver area. Second, another analysis of the same air pollution data set revealed that socioeconomic status measured at the community level did not modify association between air pollution and mortality in Vancouver (Villeneuve et al. In press). Third, adjustment for individual characteristics such as maternal age, parity, and time period of birth did not attenuate the risk estimates, providing evidence against the possibility of residential confounding. In addition, we controlled for month of birth to avoid seasonal bias. Maternal smoking is a well-known risk factor for adverse pregnancy outcomes, but it is unlikely to be associated with air pollution independently from maternal socioeconomic status. Other unmeasured factors may vary over the study period, although it is not clear to what extent these factors might confound the observed association between gaseous air pollution and adverse birth outcomes.

Our estimates of individual exposure to air pollution were based on average measures for residents living in proximity of air monitoring stations. Therefore, individual maternal exposure is inevitably misclassified. However, such misclassification is most likely random, leading to underestimation of the actual effects of air pollution (Burnett et al. 2000; Dolk et al. 2000). Variation in exposure to ambient air pollution due to residential mobility is also likely to lead to random exposure misclassification and underestimation of risk. A further complication of using the ecologic measurements of ambient air pollution over a 13-year period is that although mothers may be exposed to similar levels of air pollution at the same point in time, considerable daily and seasonal variation exists. Despite these well-recognized sources of exposure misclassification, which can be expected to bias risk estimates toward the null value of zero, associations between ambient air pollution and adverse birth outcomes observed in this study are unlikely to be due to chance.

Other studies have found that LBW, preterm birth, or IUGR is also associated with $PM_{10}$. However, this difference can be related to the availability of measurements of particulate air pollution. We only have 5 years of data available on $PM_{10}$, and our analysis did not indicate its association with any indicator of the birth outcomes under study. This negative finding may be due to the small number of live births over the 5-year period. In our study, $SO_2$ demonstrated the strongest association with IUGR. Sulfur oxides may be a

**Table 3.** Pearson correlation coefficients among daily average concentrations of gaseous air pollutants, Vancouver, 1985–1998.

| Pollutant | $SO_2$ | $NO_2$ | CO | $O_3$ |
|---|---|---|---|---|
| $SO_2$ | 1.00 | | | |
| $NO_2$ | 0.61* | 1.00 | | |
| CO | 0.64* | 0.72* | 1.00 | |
| $O_3$ | –0.35* | –0.25* | –0.49* | 1.00 |

*$p$-Value < 0.0001.

**Table 4.** Crude and adjusted ORs and 95% CIs for LBW attributable to maternal exposure to $SO_2$, $NO_2$, CO, and $O_3$ by month of pregnancy.

| Pollutant | Period of pregnancy | Crude OR (95% CI)[a] | Adjusted OR (95% CI)[a,b] |
|---|---|---|---|
| $SO_2$ | First month | 0.95 (0.89–1.02) | 1.11 (1.01–1.22) |
| | Last month | 0.99 (0.92–1.07) | 0.98 (0.89–1.08) |
| $NO_2$ | First month | 0.96 (0.90–1.01) | 0.98 (0.90–1.07) |
| | Last month | 0.99 (0.93–1.06) | 0.94 (0.85–1.04) |
| CO | First month | 1.01 (0.96–1.06) | 1.01 (0.93–1.09) |
| | Last month | 1.04 (0.98–1.09) | 0.96 (0.88–1.04) |
| $O_3$ | First month | 1.07 (1.02–1.12) | 1.04 (0.95–1.13) |
| | Last month | 1.03 (0.98–1.07) | 1.01 (0.92–1.11) |

[a]ORs were estimated based on a certain increase of pollutant: $SO_2$, 5.0 ppb; $NO_2$, 10.0 ppb; CO, 1.0 ppm; $O_3$, 10.0 ppb.
[b]Adjusted for maternal age, parity, infant sex, gestational age, and season of birth.

**Table 5.** Crude and adjusted ORs and 95% CIs for preterm birth attributable to maternal exposure to $SO_2$, $NO_2$, CO, and $O_3$ by month of pregnancy.

| Pollutant | Period of pregnancy | Crude OR (95% CI)[a] | Adjusted OR (95% CI)[a,b] |
|---|---|---|---|
| $SO_2$ | First month | 1.00 (0.95–1.06) | 0.95 (0.88–1.03) |
| | Last month | 1.06 (0.99–1.13) | 1.09 (1.01–1.19) |
| $NO_2$ | First month | 0.95 (0.91–1.00) | 1.01 (0.94–1.07) |
| | Last month | 1.08 (1.01–1.14) | 1.08 (0.99–1.17) |
| CO | First month | 0.99 (0.95–1.03) | 0.95 (0.89–1.01) |
| | Last month | 1.09 (1.04–1.15) | 1.08 (1.01–1.15) |
| $O_3$ | First month | 1.08 (1.04–1.12) | 0.98 (0.89–1.03) |
| | Last month | 1.00 (0.97–1.04) | 0.93 (0.86–1.00) |

[a]ORs were estimated based on a certain increase of pollutant: $SO_2$, 5.0 ppb; $NO_2$, 10.0 ppb; CO, 1.0 ppm; $O_3$, 10.0 ppb.
[b]Adjusted for maternal age, parity, infant sex, birth weight, and season of birth.

good indirect measure of small respirable particles that may underlie the observed association with IUGR.

The timing and intensity of exposure to gaseous pollutants such as $SO_2$ and CO during pregnancy are important in understanding the mechanisms by which adverse birth outcomes are induced. Although a range of social and behavioral determinants have been identified, neither the biologic mechanisms leading to LBW, preterm delivery, and retarded fetal growth nor the critical period of vulnerability is as yet well understood (Berkowitz and Papiernik 1993; Kramer 1987), and it is generally believed that different mechanisms may be involved at different stages of pregnancy. The observation that maternal alcohol consumption and cigarette smoking in pregnancy affect birth outcome suggests that exposures during early or late gestational period are very important.

Acute effects that provoke premature labor are not the only mechanisms by which adverse health outcomes may be induced. Chronic exposure and associated adverse birth effects could be considered for the following reasons. First, the known determinants of preterm birth include intrauterine infection (Berkowitz and Papiernik 1993; Kramer 1987). Previous studies have indicated that maternal illness due to respiratory infection during pregnancy may also be involved, although most of them focused on genitourinary infections (Gibbs et al. 1992). Second, air pollution may affect DNA or its transcription. DNA adducts have commonly been observed in areas with high levels of pollution, with placental DNA adducts more common among mothers exposed to high levels of outdoor air pollution (Perera et al. 1998, 1999; Petruzzelli et al. 1998; Topinka et al. 1997). There may be a link between DNA adducts and fetal growth: Newborns with more adducts have lower birth weight and length (Perera et al. 1998). The effects of air pollution on DNA adduct levels seem similar to the effects of cigarette smoking (Petruzzelli et al. 1998; Topinka et al. 1997). Third, the potential mechanisms could be related to hematologic factors. There are reports of increased blood viscosity and plasma fibrinogen (related to blood coagulation) during air pollution episodes (Peters et al. 1997). Rheologic variables, including blood viscosity, influence blood perfusion of the placenta (Peters et al. 1997; Petruzzelli et al. 1998), and one could speculate that chronic exposure to high pollution levels may influence placental functions. In addition, it is postulated there is a parallel with maternal smoking, an established risk factor for LBW (Windham et al. 1999, 2000), despite the fact that the underlying biologic mechanisms of toxicity are not well understood. Although the fetal exposures to air pollution are probably much lower than to constituents of cigarette smoke, the biologic mechanisms such as rheologic factors and DNA damage may be somewhat similar. Although a full understanding of biologic mechanisms is important in understanding the effects of environmental health hazards such as air pollution and cigarette smoke, the lack of a confirmed mechanistic hypothesis does not preclude a meaningful epidemiologic assessment of risk.

The time, intensity, and duration of the adverse factors affecting fetal growth will manifest themselves in different ways. Peak growth in fetal length occurs first, around the 20th week of gestation, whereas peak growth in weight occurs around the 33rd week of gestation (Falkner 1986). It is also estimated that by the 28th week, a fetus has reached 71% of the mean length at 41 weeks, whereas weight is only 32% of full-term infant weight. Thus, growth in length is determined predominantly in the first two trimesters. In the present study we consistently found that maternal exposures to $SO_2$ and CO during early pregnancy are the best predictors of early fetal adverse development. The effects of air pollution on pregnancy outcomes may differ with the timing of exposure, with early exposures likely to be more important for pregnancy end points such as spontaneous abortion and birth defects (Antipenko and Kogut 1993; Hansteen et al. 1987). A recent study (Ritz et al. 2002) evaluated the effects of air pollution on the occurrence of birth defects in neonates and fetuses in Southern California during the period 1987–1993. In that study, the risk of cardiac ventricular, aortic artery and valve defects, and pulmonary artery and valve anomalies increased with maternal CO and $O_3$ exposures during the second month of pregnancy, representing a link between air pollution and human malformation during a vulnerable window of development. Thus, maternal exposure to air pollution during pregnancy may also affect other pregnancy end points such as spontaneous abortion, fetal growth, and even fetal death.

To a certain extent, effects during early pregnancy are consistent with current knowledge on the etiology of IUGR. Nutrient and oxygen supply to the fetus during gestation are key factors in fetal development. Several new findings on this topic suggest that the pathogenesis resulting in IUGR is triggered by an abnormal reaction between trophoblast and uterine tissues in the first few weeks of pregnancy (Duvekot et al. 1995; Khong et al. 1986). The altered growth may arise from defective trophoblast invasion, resulting in placental implantation and maternal hemodynamic maladaptation (Duvekot et al. 1995; Roberts et al. 1991). These changes could result in reduced growth and fetal adaptation to undernutrition, with subsequent changes in the structure and function of a range of organs and tissues (Barker et al. 1993; Godfrey et al. 1996). Because ultrasound studies (Greisen 1992) have shown that preterm infants weigh

**Table 6.** Crude and adjusted ORs and 95% CIs for IUGR attributable to maternal exposure to $SO_2$, $NO_2$, CO, and $O_3$ by month of pregnancy.

| Pollutant | Period of pregnancy | Crude OR (95% CI)[a] | Adjusted OR (95% CI)[a,b] |
|---|---|---|---|
| $SO_2$ | First month | 1.07 (1.02–1.12) | 1.07 (1.01–1.13) |
| | Last month | 1.01 (0.96–1.06) | 1.00 (0.94–1.06) |
| $NO_2$ | First month | 1.06 (1.02–1.10) | 1.05 (1.01–1.10) |
| | Last month | 0.97 (0.92–1.02) | 0.98 (0.92–1.03) |
| CO | First month | 1.06 (1.02–1.10) | 1.06 (1.01–1.10) |
| | Last month | 0.97 (0.91–1.05) | 0.98 (0.94–1.03) |
| $O_3$ | First month | 0.98 (0.95–1.01) | 0.99 (0.93–1.04) |
| | Last month | 0.99 (0.96–1.02) | 0.99 (0.94–1.04) |

[a]ORs were estimated based on a certain increase of pollutant: $SO_2$, 5.0 ppb; $NO_2$, 10.0 ppb; CO, 1.0 ppm; $O_3$, 10.0 ppb. [b]Adjusted for maternal age, parity, infant sex, and season of birth.

**Table 7.** ORs and 95% CIs for IUGR attributable to maternal exposure to $SO_2$, $NO_2$, CO, and $O_3$ by trimester of pregnancy.

| Pollutant | Period of pregnancy | Crude OR (95% CI)[a] | Adjusted OR (95% CI)[a,b] |
|---|---|---|---|
| $SO_2$ | 1st trimester | 1.07 (1.01–1.14) | 1.07 (1.00–1.14) |
| | 2nd trimester | 0.98 (0.92–1.04) | 0.98 (0.91–1.04) |
| | 3rd trimester | 1.02 (0.96–1.09) | 1.03 (0.96–1.10) |
| $NO_2$ | 1st trimester | 1.04 (0.99–1.10) | 1.03 (0.98–1.10) |
| | 2nd trimester | 0.96 (0.91–1.01) | 0.94 (0.88–1.00) |
| | 3rd trimester | 0.96 (0.91–1.02) | 0.98 (0.92–1.06) |
| CO | 1st trimester | 1.06 (1.01–1.10) | 1.05 (1.00–1.10) |
| | 2nd trimester | 0.97 (0.94–1.01) | 0.97 (0.92–1.01) |
| | 3rd trimester | 0.97 (0.93–1.01) | 0.97 (0.93–1.02) |
| $O_3$ | 1st trimester | 0.99 (0.96–1.03) | 1.02 (0.95–1.08) |
| | 2nd trimester | 1.04 (1.00–1.08) | 1.08 (1.01–1.15) |
| | 3rd trimester | 1.01 (0.97–1.05) | 0.99 (0.93–1.06) |

[a]ORs were estimated based on a certain increase of pollutant: $SO_2$, 5.0 ppb; $NO_2$, 10.0 ppb; CO, 1.0 ppm; $O_3$, 10.0 ppb. [b]Adjusted for maternal age, parity, infant sex, and season of birth.

less than infants who remain *in utero* at the same gestational age, a fetus with restricted growth may exhibit a greater susceptibility to events that trigger premature labor. CO may interfere with metabolic and transport functions of the placenta and, after crossing the placental barrier, concentrates more in the fetus than in the mother.

It is important to recognize that ambient air pollution is a complex mixture involving multiple components. In the present study, associations between individual gaseous pollutants and adverse pregnancy outcomes tended to persist after adjustment for copollutant exposure in multiple-pollutant models. Overall, the associations among $SO_2$ and LBW, preterm birth, and IUGR appear to be most robust against copollutant adjustment. These results suggest that the effects of air pollutants on birth outcomes are likely related to more than one component of the complex mix of air pollutants present in urban environment.

In summary, our data from Vancouver, Canada, confirm previous reports from China, Europe, and the United States about the adverse effects of ambient air pollution on birth outcomes. Although there are some differences in strength of these associations, it is increasingly evident that relatively low concentrations of ambient air pollution are associated with adverse birth outcomes in populations experiencing diverse air pollution profiles. Although the mechanisms underlying these associations are not yet clear, these effects require further examination in other populations. Further research also needs to be conducted with more detailed information on personal exposures, effect modifiers, and other adverse pregnancy outcomes such as birth defects and spontaneous abortion.

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