Association between Air Pollution and Intrauterine Mortality in São Paulo, Brazil

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The associations among daily counts of intrauterine mortality and pollutant concentrations (NO_2, SO_2, CO, O_3, and particulate matter ≤ 10 μm) were investigated for the period ranging from January 1991 to December 1992 in the city of São Paulo, Brazil. We used Poisson regression techniques, adjusted for season and weather. The association between intrauterine mortality and air pollution was strong for NO_2 (coefficient = $0.0013/\mu g/m^3$; $p < 0.01$) but lesser for SO_2 (coefficient = $0.0005/\mu g/m^3$; $p < 0.10$) and CO (coefficient = $0.0223/ppm$; $p < 0.10$). A significant association was observed when an index that combined these three pollutants was considered in the models instead of considering each pollutant individually ($p < 0.01$). These associations exhibited a short time lag, not over 5 days. In addition, some evidence of fetal exposure to air pollution was obtained by disclosing a significant association between the levels of carboxyhemoglobin of blood sampled from the umbilical cord and ambient CO levels in children delivered by nonsmoking pregnant women in the period from May to July 1995. Our results suggest that air pollution in São Paulo may promote adverse health effects on fetuses. *Key words:* air pollution, carboxyhemoglobin, fetus environmental exposure, intrauterine mortality. *Environ Health Perspect* 106:325–329 (1998). [Online 5 May 1998]
http://ehpnet1.niehs.nih.gov/docs/1998/106p325-329pereira/abstract.html

Although adverse effects of air pollution on human health have been clearly demonstrated (1–8), there are still some important questions that have not been fully clarified. Most of the previous studies have examined the association between measurements of air pollution and mortality from all causes at different ages. Available evidence suggests that specific age groups may be more susceptible to air pollution (9–11) than others. However, a critical aspect of the age-dependent susceptibility to air pollution—the possible effects of air pollution on fetuses—has not yet been explored.

The idea that airborne insults may interfere with pregnancy seems to be plausible because the effects of maternal smoking on fetuses are well documented in the literature (12). In this context, the hypothesis that air pollution may interfere with pregnancy, especially those considered high risk, is plausible, but not fully addressed. Atmospheric pollution in São Paulo is high enough to induce adverse health effects on experimental animals. Previous studies using rats as sentinel animals for assessing the chronic effects of air pollution disclosed functional alterations of mucociliary clearance, inflammatory changes along the respiratory tract, and bronchial hyperresponsiveness in exposed animals (13–16). More recently, we reported a significant promoter effect of air pollution on the development of experimentally induced lung tumors in mice (17). These experimental findings provide some degree of toxicological support to epidemiological studies that indicate a significant association between air pollution and mortality in São Paulo (10,11).

Given the magnitude of the air pollution problem in São Paulo, an environmental state agency, the São Paulo air pollution controlling agency (CETESB), monitors air quality through a network of 12 stations. In addition, São Paulo has a large population (about 16,000,000 in the metropolitan area), and daily mortality counts are provided by a special service (municipal mortality information improvement program; PROAIM) administered by the municipal government. Given the combination of such characteristics, São Paulo may be considered a suitable place to study the health effects of air pollution on epidemiological grounds, especially when counts of rare events such as fetal mortality are considered as point of interest.

This work presents the results of a time–series study relating air pollution and intrauterine mortality in São Paulo from 1991 to 1992.

Materials and Methods

Daily counts of intrauterine mortality (for fetuses over 28 weeks of pregnancy age) in the city of São Paulo, from January 1991 to December 1992, were provided by PROAIM. These deaths were registered as intrauterine by the attending physician in the special field of the death certificate employed in Brazil at the moment of delivery of the fetus. The intrauterine mortality counts for fetuses under 28 weeks were not collected due to a lack of information in such registries. According to the Brazilian legislation, late fetal loss is assigned by one of these three parameters: age of pregnancy over 28 weeks, weight over 1,000 g, and fetal length over 35 cm. In these cases, the death certificate must be done; the death certificate is not compulsory for cases that do not meet criteria.

The city of São Paulo air pollution controlling agency (CETESB) provides daily records of NO_2, SO_2, CO, O_3, and particulate matter ≤ 10 μm (PM_{10}) concentrations (18,19). Values of pollutants available in each station were collected, averaged, and considered as indicative of the citywide status. Information on daily temperature and humidity were also obtained at CETESB. Not all stations measure all pollutants, as shown in Table 1.

The association between daily intrauterine deaths and pollutant concentrations, as well as weather variables, was evaluated by Poisson regression models, using the daily number of intrauterine deaths as the dependent variable. The daily concentration of pollutants in combination with terms accounting for season and weather were simultaneously considered as independent variables: 24 dummy variables representing each month of the period of study, 7 variables representing each day of the week; the lowest temperature of the day; the relative humidity measured at 1200 hr; four indicators for the lowest temperature of the day ($<13.50°C$, $13.50°C$ $-15.60°C$, $15.60°C-17.55°C$, $>17.55°C$);

Table 1. Description of the number of stations, method of analysis, and the time of the day employed when pollutant samples were collected

Pollutants	Number of stations	Analysis method	Time collected
PM_{10} (mg/m^3)	13	Beta monitor	24 hr mean (beginning at 1600 hr of the preceding day)
NO_2 (mg/m^3)	4	Chemiluminescence	24 hr mean (beginning at 1600 hr of the preceding day)
O_3 (mg/m^3)	4	Chemiluminescence	Major hour mean (beginning at 1600 hr of the preceding day)
SO_2 (mg/m^3)	14	Coulometry	24 hr mean (beginning at 1600 hr of the preceding day)
CO (ppm)	5	No dispersive infrared	The highest 8-hr moving average (beginning at 1600 hr of the previous day)
Temperature (°C)	1		The lowest daily temperature
Relative humidity (%)	1		Measured at 1200 hr

PM_{10}, particulate matter ≤10 µm.

and four indicators for humidity (<59.0%, 59.0%–67.5%, 67.5–76.5%, >76.5%).

Using models with different lags and moving averages, we assigned equal weights for the days considered in the different time windows from 2 to 14 days. For example, in a 3-day lagged moving average, we computed the average pollution level of the concurrent day and the preceding 2 days. We adopted the 5-day moving average for NO_2, a 3-day moving average for CO, and the mean of the concurrent day for SO_2, according to the highest regression coefficient and statistical significance.

Considering the marked degree of interdependence of the pollutants present in the urban atmosphere, we developed an index of overall pollution (IOP) using the pollutants that presented significant associations with intrauterine mortality.

$$IOP = \frac{\left[\left(\dfrac{NO_{2d}}{\overline{NO_2}}\right) + \left(\dfrac{CO_d}{\overline{CO}}\right) + \left(\dfrac{SO_{2d}}{\overline{SO_2}}\right)\right]}{3} \quad (1)$$

where d = daily mean level and $\overline{NO_2}$, $\overline{CO}$, and $\overline{SO_2}$ = the biannual mean of respective pollutants.

Thus, the IOP reflects variations of air pollution concentrations and may be used as a proxy variable of total exposure, a parameter that may be needed when it is difficult to ascribe to a single pollutant a health effect that is detected in a complex group of environmental pollutants, which all may be significant. New models were built using different lags and moving averages of the IOP.

Because we obtained significant associations between intrauterine mortality and some pollutants, we designed a second study with the intention of obtaining some evidence of fetal exposure to ambient levels of pollution. We selected the levels of carboxyhemoglobin (COHb) in fetal blood as an estimator of exposure to ambient pollution (expressed in terms of CO) because of the relative stability of the ligation between fetal hemoglobin to CO and because of the feasibility of determining reliable COHb

measurements. For this purpose, samples of cord blood were collected from 47 healthy nonsmoking pregnant women. This sampling was conducted from May to July 1995 at the Santa Joana Hospital, which is in the central region of São Paulo. The samples of venous blood were collected from the umbilical cord soon after delivery and kept in vacutainer tubes with heparin. The levels of COHb were measured by spectrophotometry methods described by Katsumata et al. (20) and Beutler and West (21). The daily atmospheric concentration of CO in São Paulo was provided by five stations of the CETESB for the same period. We considered the average of the five monitoring stations as representative of the citywide status. Due to a lack of NO_2 measurements by the CETESB in this period, we did not attempt to evaluate the association between this pollutant and methemoglobin levels in the blood samples.

These data were analyzed by multiple linear regression models using M-estimation techniques. Briefly, M-estimation techniques are weighted regression procedures

Table 2. Pairwise Pearson correlation coefficients among the main variables of the study

	Intrauterine deaths	NO_2	SO_2	CO	PM_{10}	Ozone	Temperature
NO_2	0.08*						
SO_2	0.05	0.41**					
CO	0.15**	0.24**	0.34**				
PM_{10}	0.02	0.45**	0.74**	0.41**			
Ozone	0.00	0.17**	0.15**	0.04	0.25**		
Temperature	0.09**	0.07	-0.19**	0.11**	-0.14**	0.18**	
Humidity	0.03	-0.31**	-0.33**	-0.06	-0.43	-0.35**	-0.07

PM_{10}, particulate matter ≤10 µm.
*$p<0.05$; **$p<0.01$.

Table 3. Descriptive statistics for the main variables in the analyses

	Mean ± SD	Minimum	Maximum	Number of days
Intrauterine mortality counts	8.36 ± 3.08	1.00	18.00	731
Pollutants				
NO_2 (mg/m^3)	157.09 ± 81.02	2.30	668.30	704
SO_2 (mg/m^3)	18.90 ± 8.53	3.80	59.70	730
CO (ppm)	5.73 ± 1.89	1.30	12.50	726
PM_{10} (mg/m^3)	65.04 ± 27.28	14.80	192.80	730
O_3 (mg/m^3)	67.50 ± 45.04	2.70	272.00	727
Weather variables				
Temperature (°C)	15.37 ± 2.72	5.55	20.30	730
Relative humidity (%)	68.38 ± 11.55	42.50	100.00	730

Abbreviations: SD, standard deviation; PM_{10}, particulate matter ≤10 µm.

that attribute different weights to each point considered in the regression model to minimize the influence of heterocedasticity and outlying points on parameter estimates (22). The choice of robust regression was used to minimize the possibility that regression coefficients and their significance would be biased by outliers in a relatively limited sample. We considered the COHb level to be the dependent variable. CO levels on the day of delivery, weight of the newborn, and a dummy variable that indicated passive smoking were used as independent variables. We defined passive smoking as the exposure to an environment where there were smokers, at work or at home.

To verify if the association between COHb and CO was dose dependent, we used a regression model with three dummy variables, corresponding to the categories based on the tertiles of CO instead of on the continuous pollutant variable.

Results

First study. Pairwise Pearson correlation coefficients relating the number of daily

Table 4. Estimated Poisson regression coefficients and standard errors with NO_2 included in the model

| Variables	Estimated coefficients	Standard error
Pollutant		
NO_2 (mg/m^3)	0.0013**	0.00
Months of year indicators		
February 1991	-0.07	0.09
March 1991	-0.04	0.08
April 1991	-0.19*	0.09
May 1991	-0.15	0.09
June 1991	-0.21*	0.10
July 1991	-0.24*	0.11
August 1991	-0.46**	0.11
September 1991	-0.28**	0.10
October 1991	-0.20**	0.09
November 1991	-0.27**	0.09
December 1991	-0.33**	0.09
January 1992	-0.08	0.08
February 1992	-0.26**	0.09
March 1992	-0.18*	0.09
April 1992	-0.22**	0.09
May 1992	-0.36**	0.10
June 1992	-0.44**	0.10
July 1992	-0.50**	1.11
August 1992	-0.39**	0.10
September 1992	-0.31**	0.10
October 1992	-0.40**	0.13
November 1992	-0.18	0.13
December 1992	-0.11	0.12
Day of week indicators		
Monday	0.17**	0.05
Tuesday	0.26**	0.05
Wednesday	0.28**	0.05
Thursday	0.26**	0.05
Friday	0.23**	0.05
Saturday	0.15**	0.05
Weather variables		
Relative humidity (ma 2 days)	-0.01	0.02
Low temperature (ma 2 days)	0.00	0.00
Weather indicators		
Relative humidity		
<59.0 %	0.00	0.00
≥59.0 and <67.5 %	0.08	0.05
≥67.5 and <76.5 %	0.04	0.07
≥76.5 %	0.03	0.12
Low temperature		
<13.50 °C	0.00	0.00
≥13.50 and <15.60 °C	0.00	0.06
≥15.60 and <17.55 °C	0.01	0.09
≥17.55 °C	0.03	0.12
Intercept	2.00	0.31

ma, moving average.
*$p<0.05$; **$p<0.01$.

intrauterine deaths, pollutant concentrations, and weather variables are presented in Table 2. Table 3 shows descriptive measures [mean, standard deviation (SD), minimum and maximum values, and the number of days in the period of study along with available information] of the variables under investigation.

Table 4 depicts the coefficients of the Poisson regression model and suggests a significant association between intrauterine mortality and NO_2. This association was also evident when ordinary least squares regression models were employed.

Table 5. Estimated regression coefficients and standard errors for all pollutants when considered both separately and simultaneously in the completed model[a]
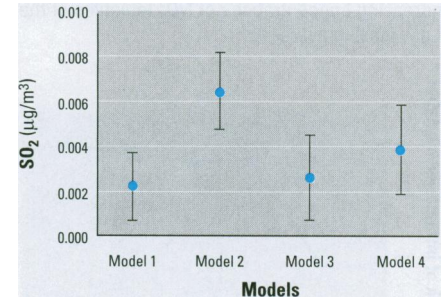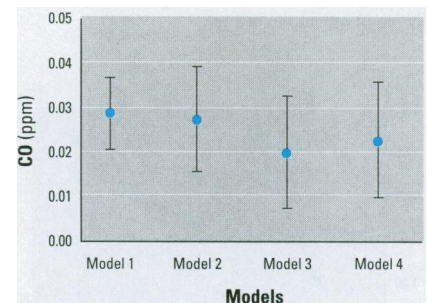
Pollutants	Separately		Simultaneously	
	Coefficient	Standard error	Coefficient	Standard error
NO_2 (mg/m^3)	0.0013**	0.0003	0.0012**	0.0004
SO_2 (mg/m^3)	0.0038***	0.0020	0.0029	0.0031
CO (ppm)	0.0223***	0.0132	0.0076	0.0158
PM_{10} (mg/m^3)	0.0008	0.0006	-0.0005	0.0010
O_3 (mg/m^3)[a]	0.0000	0.0004	0.0002	0.0004

PM_{10}, particulate matter ≤10 μm.
**$p<0.01$; ***$p<0.10$.
[a]Independent variables included in the models are 23 indicator variables for month and year, 6 indicator variables for day of week, 2-day moving averages of temperature and humidity, and 3 indicator variables each for temperature and humidity.
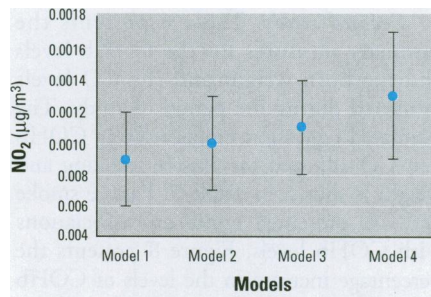
Figure 1. Regression coefficients and standard errors for NO_2 (5-day moving average) across different model specifications of independent variables. Models: Model 1, NO_2; Model 2, Model 1 plus months; Model 3, Model 2 + days of the week; Model 4, Model 3 + weather.

Figure 2. Regression coefficients ± standard errors for SO_2 (daily mean) across different model specifications of independent variables. Models: Model 1, NO_2; Model 2, Model 1 plus months; Model 3, Model 2 + days of the week; Model 4, Model 3 + weather.

Figure 3. Regression coefficients ± standard errors for CO (3-day moving average) across different model specifications of independent variables. Models: Model 1, NO_2; Model 2, Model 1 plus months; Model 3, Model 2 + days of the week; Model 4, Model 3 + weather.

SO_2 and CO exhibited a marginal association with intrauterine mortality, but only when Poisson regression was employed. In Table 5 we present the Poisson coefficients and standard errors (SE) for all pollutants, when included separately or simultaneously in the model adjusted for season and weather. No significant association was detected between particulate matter ≤10 μm (PM_{10}) or ozone and intrauterine mortality.

When all the pollutants were included simultaneously in the model, the association between intrauterine mortality and NO_2 remained significant (Table 5).

The sensitivity of the association between intrauterine mortality and NO_2 was evaluated via models with different specifications of the independent variables. To the basic univariate model (model 1 in Figs. 1–3), we included, in a progressive way, 23 indicator variables for month and year, 6 indicator variables for day of week, 2-day moving averages of temperature and humidity, and 3 indicator variables each for temperature and humidity. The coefficient for NO_2 increased slightly with the inclusion of more controlling variables (Fig. 1), whereas the coefficients for SO_2 and CO remained relatively stable across different model specifications (Fig. 2 and Fig. 3).

Regression models using intrauterine mortality as the dependent variable and 23 indicator variables for month and year, 6 indicator variables for day of the week, 2-day moving averages of temperature and humidity, and 3 indicator variables each for temperature and humidity, in which five categories of NO_2 (quintiles) concentrations were used as dummy variables instead of the continuous pollution variable, suggested that the relative risk of intrauterine death was dose dependent for NO_2 (Fig. 4). In the same way, Figure 5 and 6 show the relative risk of intrauterine death when five categories of SO_2 and CO
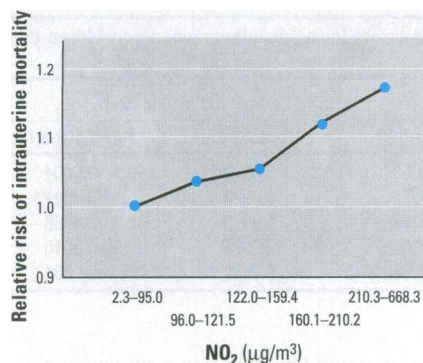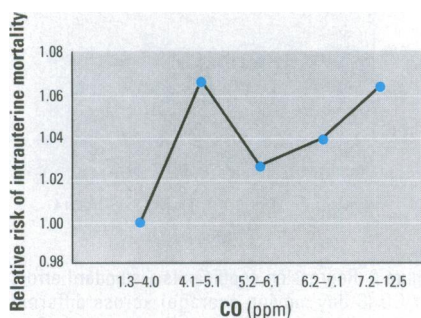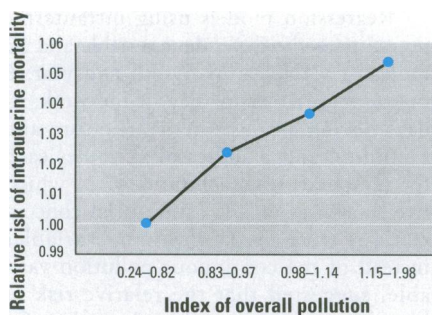
Figure 4. Relative risk of intrauterine mortality for increasing concentrations of NO_2 (quintiles of the 5-day moving average).
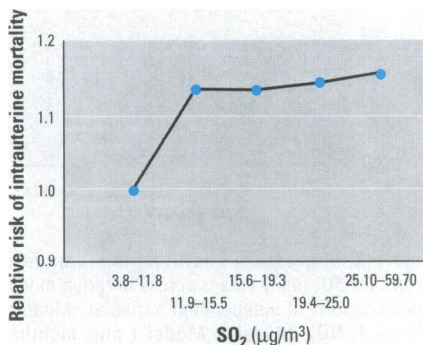
Figure 5. Relative risk of intrauterine mortality for increasing concentrations of SO_2 (quintiles of the daily mean moving average).

Figure 6. Relative risk of intrauterine mortality for increasing concentrations of CO (quintiles of the 3-day moving average).

Figure 7. Relative risk of intrauterine mortality for increasing concentrations of the index of overall pollution in the study.

concentrations were included. CO does not seem to present a dose-dependent behavior.

In fact, the most robust association was observed when IOP (the average of the rates of variation of NO_2, CO, and SO_2) was considered in the models instead of as single pollutants. A significant ($p<0.001$) and dose-dependent relationship with intrauterine mortality was detected (Fig. 7), with the best signal coming from the 3-day moving average of this pollution index. Interestingly enough, the association between IOP and intrauterine mortality was almost linear, with no evidence of a safe threshold.

Second study. Table 6 presents the summary measures for the COHb levels and newborn weight and the CO levels measured during the period of study. The estimated regression model relating COHb and CO adjusted for passive smoking and weight is shown in Table 7. Passive smoke and CO presented significant associations with COHb levels. Figure 8 presents the percentage increase in the levels of COHb in the blood of fetuses as a function of categories of environmental CO (formed based on the tertiles). This figure suggests that the association between COHb and CO levels may be dose dependent.

This finding suggests that the levels of COHb are influenced by outdoor concentration of CO for nonsmoking women and may interfere with the oxygen levels in the fetuses.

Discussion

Our results showed a significant and robust association between air pollution and intrauterine mortality in São Paulo for the period from January 1991 to December 1992. NO_2 was more significantly associated with this adverse health effect than other pollutants. This association was significant, despite the several controlling variables employed in the modeling procedures (Table 4 and Fig. 1), and exhibited dose-dependent behavior (Fig. 4). The observed association is in agreement with that of previous studies that showed a significant association between mortality due to respiratory causes and NO_x in children (10). The other pollutants associated with intrauterine mortality were SO_2 and CO, but the corresponding associations were more sensitive to the specifications of the models and did not seem to present dose-dependent behavior.

Considering the high degree of correlation between the concentrations of all the pollutants (Table 3), it is very difficult to ascribe the observed adverse health effect to a single pollutant. Thus, whether our results are dependent on intrinsic NO_2, SO_2, or CO effects or, alternatively, whether these three pollutants represent proxy variables for the complex automotive emission products is a point that is still to be clarified. In fact, the most robust association was observed when an index of air pollution, which combined the three pollutants associated with mortality, was used in the modeling (Fig. 7).

Although there are intrinsic limitations in ecological studies, the association between air pollution and mortality that we detected seems robust enough to be considered biologically significant. First of all, this positive association was stable across different model specifications and when

Table 6. Descriptive statistics of the main variables used to relate CO to carboxyhemoglobin (COHb) in fetuses

| Variable | Valid cases | Mean ± standard deviation | | |
		Passive smoke +	Passive smoke -	Total
COHb (%)	47 (26, 21)	1.42 ± 0.78	1.39 ± 0.98	1.41 ± 0.87
Weight (kg)	47 (26, 21)	3.35 ± 0.32	3.24 ± 0.31	3.30 ± 0.32
CO (ppm) [a]	47 (26, 21)	5.57 ± 1.87	6.03 ± 2.57	5.93 ± 2.20

[a] Mean of ambient CO level based on the day of delivery.

Table 7. Coefficients and standard errors for the M-estimation regression model to carboxyhemoglobin, the dependent variable of passive smoking (%); body weight at birth; and ambient CO levels

Variable	Coefficient	Standard error
Passive smoke	0.85*	0.28
Weight (kg)	-0.33	0.43
CO (ppm)	0.29**	0.06
Constant	0.19	1.50

*$p<0.05$; **$p<0.01$.
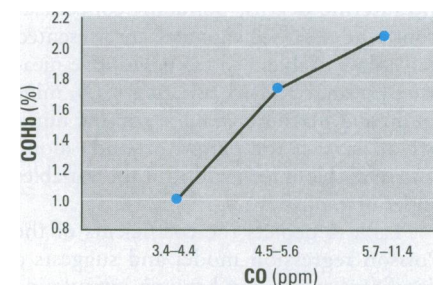
Figure 8. Relative variation of carboxyhemoglobin (COHb) as a function of CO, adjusted for passive smoking and body weight.

controlling for several weather related conditions. Secondly, the time–series approach we employed considered the same population over a relatively short time period, thus minimizing the influence of other confounding variables present in population studies. In addition, there is evidence supporting the biologic plausibility of an association between air pollution and fetal mortality. Previous studies have demonstrated the presence of toxic environmental substances in umbilical cord blood (*23*). Petr and Schmidt (*24*) suggested that atmospheric nitrogen oxides increase methemoglobin levels, which interferes with the oxygen-carrying capacity of hemoglobin in children. Infants are particularly susceptible to such events because fetal hemoglobin is more prone to be oxidized to methemoglobin (*25*).
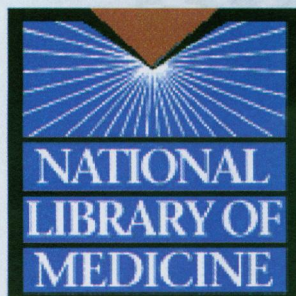
To obtain further evidence of fetal exposure to air pollution, we carried out additional studies to verify whether a marked fetal exposure to pollution was affected by outdoor levels of contamination. Unfortunately, the network of the CETESB did not provide measurements of NO_2 in 1995. Thus, we considered COHb as our fetal marker of acute pollution exposure because other studies have demonstrated that COHb levels for newborns of smoking mothers are higher than those of nonsmoking mothers (*26,27*). In this context, we conducted a second experiment by measuring the COHb levels in blood collected from the umbilical cord in 47 nonsmoking women. We performed the measurements along the period of May to July 1995. Although based on a relatively small sample ($n = 47$), we detected a significant dose-dependent relationship between CO and COHb. Our results reinforce the biological plausibility of an association between air pollution and fetal death because high levels of COHb may cause a decrease in oxygenation and may even lead to death.

The association between air pollution and fetal mortality that we detected is somewhat surprising. If this association is true, there may be fetuses with a greater susceptibility to injury such that a small decrease in oxygenation may represent an event that can lead to death. In this case, we postulate that fetuses at imminent risk of dying may represent the preferential target of air pollution injury, especially if we consider the short time lag between the increase in air pollution and death observed in our study.

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