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Association between Air Pollution and Mortality Due to Respiratory Diseases in Children in São Paulo, Brazil: A Preliminary Report

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This work presents the results of a time series study relating air pollution and respiratory mortality in children under 5 years of age in the metropolitan area of São Paulo, Brazil. Daily records of mortality (excluding neonatal mortality) for the period May 1990 to April 1991 were collected along with daily records of relative humidity, temperature, SO_2, CO, particulates (PM10), O_3, and NO_x concentrations. Using multiple regression methods we demonstrated a significant association between mortality due to respiratory diseases and the NO_x levels. After controlling for weather and season effects, the odds of dying due to respiratory diseases, considering the mean levels of NO_x in São Paulo, was estimated at 1.3 (±0.13). This result is in accord with previous animal studies conducted by our group and indicates that air pollution in São Paulo has reached levels high enough to have adverse health effects on the exposed population.

INTRODUCTION

Critical episodes of air pollution have been unequivocally associated with a significant increase in mortality (Firket, 1936; Her Majesty's Public Health Service, 1954; U.S. EPA, 1982; Wichman *et al.*, 1989). Studies focusing on the effects of nonepisode concentrations of pollutants on health have also shown a positive association between mortality and pollution (Schimmel, 1978; Mazumdar *et al.*, 1982; Fairley, 1990; Schwartz and Marcus, 1990; Schwartz, 1991; Schwartz and Dockery, 1992a,b; Pope *et al.*, 1992). These studies indicate that the effects of pollution on mortality may occur in doses below the adopted standards of air quality with no evidence of a threshold.

The association between general mortality and air pollution levels has not yet been fully clarified. Although acute episodes are related to respiratory deaths, nonepisode events are reported to be related to cardiovascular mortality, mainly among elderly people. These findings suggest that pollution-related mortality manifests mainly among those that are at imminent risk of dying. Moreover, recent evidence indicates not only that the health of people with chronic diseases is affected by air pollution, but also that the prevalence of respiratory illness in children increases with low levels of air contamination (Dockery *et al.*, 1989).

If pollution increases respiratory morbidity, it conceivably could also contribute to mortality due to respiratory diseases in children. However, this latter point

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was not hitherto demonstrated, perhaps because in places where there is high child mortality (such as the large urban conglomerates of the underdeveloped countries) it is relatively difficult to obtain data on both air contaminants and health statistics.

Unfortunately for its inhabitants, the metropolitan area of São Paulo (henceforth called São Paulo) meets most of the criteria for assessing the effects of air pollution on children's health. São Paulo has about 16,000,000 inhabitants spread over an area of 5000 km^2. São Paulo is the most industrialized center of Latin America and has about 3,000,000 light-duty cars and 300,000 trucks. Due to its geographical characteristics, this region is subject to frequent thermal inversions. Since air pollution is considered a serious problem in São Paulo, an environmental state agency (CETESB) measures air pollution levels by means of a telemetric monitoring network. According to CETESB, vehicle emissions are the main source of atmospheric pollution in São Paulo. In addition to the availability of air pollution data, the Municipal Government recently implemented a system (PROAIM) that provides reliable information on mortality for the entire city.

Recent studies by our group (Böhm *et al.*, 1989; Saldiva *et al.*, 1992) have also demonstrated that the air composition of São Paulo is bad enough to produce inflammatory alterations of the airways and pulmonary parenchyma in rats reared for prolonged periods downtown. As a consequence of the inflammatory process, pulmonary defenses were diminished, leading to an increased mortality due to respiratory diseases. In addition, there is some indirect support for the hypothesis that air pollution in São Paulo is affecting not only rats but also children. Respiratory diseases constitute the second most frequent cause of death in children under 5 years of age (surpassed only by neonatal causes).

This work presents the results of a time series study relating air pollution and respiratory mortality for children under 5 years of age in São Paulo, in the period 1990–1991.

MATERIAL AND METHODS

Daily records of mortality for children under 5 years of age were obtained from PROAIM for the period May 1990 to April 1991. Mortality due to congenital malformations or caused by neonatal events (International Classification of Diseases (ICD) equal to or greater than 740 and equal to or less than 779) were excluded from the study. In addition to the overall mortality, deaths caused by respiratory diseases were obtained for the same period and the same age group.

Daily records of SO_2, CO, particulates (inhalable fraction, PM10), O_3, and NO_x concentrations were obtained from CETESB. Although there are 12 monitoring stations in São Paulo, not all of them provide measurements of all pollutants listed above. In addition, there are large areas of the city not covered by any monitoring station. Since the monitoring network of CETESB was mainly designed to assess the air pollution profile of the central part of the city, we considered the average of the 10 stations more centrally located as indicative of the citywide pollution levels. The number and characteristics of the monitoring stations are presented in Table 1, along with the minimum and maximum standard deviations of the daily citywide average for each pollutant. Due to technical problems in the air pollution

TABLE 1
CHARACTERISTICS OF THE AIR POLLUTION MONITORING SYSTEM

Pollutant	Stations	Method	Min SD	Max SD
SO_2 ($\mu g/m^3$)	8	Coulometry	4.29	26.89
CO (ppm)	3	Infrared	0.00	4.04
NO_x (ppm)	3	Chemiluminescence	0.00	0.23
O_3 (ppb)	4	Chemiluminescence	1.62	22.81
PM10 ($\mu g/m^3$)	8	Beta monitor	8.48	41.01

Note. Min SD and Max SD, minimum and maximum standard deviations of the daily averages of the individual data values provided by each station, for each pollutant, during the study (May 1990–April 1991).

monitoring system, there were some missing data for all pollutants: 2 days for PM10; 3 days for CO, SO_2, and O_3; and 20 days for NO_x.

The association between daily mortality and air pollution variables was evaluated by multiple regression analysis. In order to detect a possible phase lag between the increase in air pollution and the occurrence of death, the correlation between daily mortality and the concentration of each pollutant was calculated with lags ranging from 1 to 20 days, in steps of 1 day. This procedure was also considered for temperature and humidity. In general, the estimated correlation coefficient for daily mortality and individual pollutants was very low (r values $<$ 0.3) and had a short lag effect. In general, the largest correlations with mortality were pollution concentrations of the concurrent day and the 2 subsequent days. The correlation coefficients tended to decrease with longer time lags. This result is consistent with the finding of a short lag between changes in pollution and mortality observed by Schwartz and Dockery (1992a). Since the association between mortality and pollutants was stronger within 2 days after death, we decided to use a 3-day moving average of pollutants in the analysis. The moving average was computed as follows: the average of the first 3 days of the study was ascribed to the third day, and the average of the second to the fourth day was used as the value of the fourth day, thus moving in steps of 1 day. This procedure also provided a "smoothing" of our data and helped to incorporate in the analysis periods with less than three consecutive missing data points. Periods with more than four consecutive missing points were excluded.

The respiratory mortality distribution observed in our series was somewhat skewed, with the mean (3.04 deaths/day) close to the empirical variance (4.48). This profile suggests that a Poisson distribution should be considered. For the regression models, we used as the dependent variable either the number of respiratory deaths or the transformed value of respiratory death counts, $\sqrt{\text{deaths} + 3/8}$. This latter approach is usually suggested to stabilize variance in cases where the underlaying distribution is Poisson (Anscombe, 1948). We used as independent variables the 3-day moving average of SO_2 ($\mu g/m^3$), CO (ppm), PM10 ($\mu g/m^3$), O_3 (ppb), and NO_x (ppm). Dummy variables for cold (temperature $\leq$ 8°C), hot (temperature $\geq$ 16°C), dry (relative humidity $\leq$ 55%), and humid (relative humidity $\geq$ 85%) days, season, months of the year, and days of the week

TABLE 2
MEAN (±SD) OF THE VARIABLES USED IN THE STUDY (MAY 1990–APRIL 1991)

Variable	Mean	SD
Relative humidity (%)	80.16	10.26
Temperature (°C)	15.68	3.74
SO_2 ($\mu g/m^3$)	17.10	10.13
CO (ppm)	6.18	1.45
NO_x (ppm)	0.127	0.080
O_3 (ppb)	12.14	9.94
PM10 ($\mu g/m^3$)	82.38	38.82
Respiratory deaths (daily)	3.04	2.11
Nonrespiratory deaths (daily)	5.41	2.44
Total deaths (daily)	8.45	3.40

were included in the model. In addition, mortality due to nonrespiratory causes was included as control in the regression.

RESULTS

The mean (±SD) values of the main variables along the period of study are presented in Table 2. Respiratory deaths represented about 36% of overall mortality.

Table 3 presents the Pearson correlation coefficients for the main variables used in the study. Except for O_3, the concentration of air pollutants exhibited a significant degree of interdependence. Temperature was positively associated with O_3, whereas the same effect was not observed for the remaining air pollutants.

Table 4 presents the results for the fit of the regression model. The same model was applied either using each pollutant or considering all pollutants together. The only pollutant with a significant association with respiratory mortality was NO_x ($P = 0.025$). A residual analysis using a normal plot showed no evidence against normality of the data. In fact, when the transformed respiratory mortality, $\sqrt{\text{deaths} + 3/8}$, was used instead of absolute respiratory mortality, the result of

TABLE 3
SELECTED PEARSON CORRELATION COEFFICIENTS FOR THE VARIABLES USED IN THE ANALYSIS

	Total	Resp	Nonresp	CO	SO_2	NO_x	O_3	PM10	Temp	RH
Total	1.00	0.70	0.77	0.09	0.18	0.22	−0.23	0.14	−0.30	0.04
Resp	0.70	1.00	0.10	0.09	0.17	0.17	−0.18	0.13	−0.25	0.03
Nonresp	0.77	0.10	1.00	0.03	0.09	0.15	−0.16	0.07	−0.20	0.02
CO	0.09	0.09	0.03	1.00	0.55	0.60	−0.05	0.54	−0.02	−0.04
SO_2	0.18	0.17	0.09	0.55	1.00	0.63	−0.11	0.67	−0.12	−0.24
NO_x	0.22	0.17	0.15	0.60	0.63	1.00	−0.35	0.68	−0.10	−0.03
O_3	−0.23	−0.18	−0.16	−0.05	−0.11	−0.35	1.00	−0.00	0.35	−0.35
PM10	0.14	0.13	0.07	0.54	0.67	0.68	−0.00	1.00	−0.09	−0.22
Temp	−0.30	−0.25	−0.20	−0.02	−0.12	−0.10	0.35	−0.09	1.00	−0.12
RH	0.04	0.03	0.02	−0.04	−0.24	−0.03	−0.35	−0.22	−0.12	1.00

Note. Total, total mortality; Resp, respiratory mortality; Nonresp, deaths due to nonrespiratory causes; RH, relative humidity.

TABLE 4
REGRESSION MODEL USED TO STUDY THE RELATIONSHIP BETWEEN DAILY MORTALITY DUE TO RESPIRATORY DISEASES IN CHILDREN UNDER 5 YEARS OF AGE AND AIR POLLUTION (MAY 1990–APRIL 1991)

Variable	Coefficient (deaths/day)	SE	*P* value
Intercept	4.067	0.952	0.000
Pollution variables			
CO (ppm)	−0.204	0.166	0.219
SO_2 ($\mu g/m^3 \times 100$)	−0.111	2.500	0.965
NO_x (ppm)	7.197	3.214	0.025*
O_3 (ppb × 100)	1.048	2.481	0.673
PM10 ($\mu g/m^3 \times 100$)	−0.603	0.707	0.394
Weather indicators			
Cold (temp ≤8°C)	0.823	0.887	0.354
Hot (temp ≥16°C)	0.113	0.431	0.793
Dry (RH ≤55%)	0.251	0.301	0.406
Humid (RH ≥85%)	−0.161	0.248	0.515
Season indicators			
Winter	1.146	2.083	0.484
Summer	−0.334	0.859	0.698
Fall	−0.973	1.745	0.577
Month indicators			
January	−0.442	1.071	0.680
February	−0.933	1.089	0.392
March	0.221	1.895	0.907
April	−0.246	1.850	0.894
May	2.515	1.826	0.168
June	−0.227	2.067	0.913
July	−0.886	2.069	0.669
August	−0.619	2.066	0.765
October	−0.448	0.612	0.464
November	−0.969	0.798	0.224
December	−0.496	1.120	0.658
Day-of-week indicators			
Monday	0.397	0.408	0.331
Tuesday	−0.086	0.399	0.829
Wednesday	−0.010	0.410	0.808
Thursday	−0.229	0.410	0.577
Friday	0.188	0.413	0.649
Saturday	−0.254	0.409	0.532
Nonrespiratory deaths	−0.023	0.952	0.638

the regression was basically the same, i.e., a significant association between mortality and NO_x ($P = 0.0499$). The remaining pollutants, either considered individually or together in the model, did not exhibit significant associations with mortality.

When the model presented in Table 4 was applied using nonrespiratory deaths as the dependent variable, no significant association with any pollutant was found. When the total number of deaths was used as the dependent variable (nonrespiratory deaths excluded as an independent variable in the model), a marginally significant association ($P = 0.07$) with NO_x was obtained, without contribution of

TABLE 5
COMPARISON OF REGRESSION COEFFICIENTS ACROSS DIFFERENT MODELS

Variables included	Coefficient for NO_x	*P* value
Pollutants	7.082 ± 3.023	0.019
Pollutants + Weather	7.914 ± 2.993	0.008
Pollutants + Weather + Season	7.185 ± 3.006	0.017
Pollutants + Weather + Season + Month + Day-of-week	7.160 ± 3.209	0.026
Pollutants + Weather + Season + Month + Day-of-week + Nonresp	7.197 ± 3.214	0.025

any other pollutant. This finding suggests that if any association between overall child mortality and air pollution does exist, it is dependent mostly on respiratory deaths.

Table 5 lists the estimated coefficients for NO_x studied across different models. The magnitude, as well as the significance, of the coefficients did not change considerably with the different models employed, indicating that the association between respiratory mortality and NO_x was robust relative to the several controls used in our analysis, including nonrespiratory deaths.

Table 6 presents the estimated odds (and the corresponding confidence interval) for respiratory mortality, calculated on the basis of the mean daily concentration of NO_x during the period of study. About 30% of respiratory mortality was associated with NO_x.

DISCUSSION

The results of this study indicate that mortality of children due to respiratory diseases in São Paulo was positively associated with the levels of NO_x. This association was not previously reported; most of the previous studies relating mortality to pollution described a positive association with particulates and SO_2. The effect of NO_x on child mortality seems to be specific for respiratory diseases, since deaths due to nonrespiratory events were not significantly associated with this pollutant.

The association between NO_x and respiratory mortality was quite robust. It resisted different controlling parameters, including weather and seasonal events. In addition, no consistent association between respiratory mortality and pollution was observed when NO_x was excluded from the analysis.

Although the association between respiratory mortality and pollution was described exclusively in terms of NO_x, the close interdependence between NO_x and the other pollutants (Table 3) except O_3 raises the possibility of an adverse health effect due to a single agent, especially in the complex environmental background of São Paulo. Synergic interactions ought always to be considered and possible interplay among pollutants causing respiratory damage is very difficult to exclude.

The observed lack of association between the concentration of particulates and mortality is somewhat surprising, since it was reported in previous studies (Schwartz, 1991, Schwartz and Dockery, 1992a,b; Pope *et al.*, 1992). The reasons

TABLE 6
ESTIMATED ODDS (AND CORRESPONDING 95% CONFIDENCE LIMITS) FOR CHILD MORTALITY DUE TO RESPIRATORY DISEASES BASED ON THE MEAN CONCENTRATION OF NO_x DURING MAY 1990 TO MAY 1991

Odds	Lower limit	Upper limit	*P* value
1.30	1.17	1.43	0.025

for the minor contributions of suspended particles in mortality in children clearly deserve further investigation.

Air pollution sources in São Paulo are dominated by automotive emissions. According to the data of CETESB (1991), 73% of SO_2 and 89% of NO_x emissions in São Paulo are released by automotive engines. Diesel is the fuel used by the absolute majority of the heavy-duty vehicles, whereas pure ethanol or a blend of 80% gasoline ± 20% ethanol is used to run automobiles. NO_x is present in the emissions of diesel, ethanol, and gasoline engines, whereas SO_2 is not detected in ethanol-fueled cars (Massad *et al.*, 1986). The association between NO_x and SO_2 (Table 3) suggests that fossil fuels are mainly responsible for the deterioration of the air quality in São Paulo, since both gases are present in gasoline and diesel emissions. In this context, the possibility that NO_x may be an indicator of overall automotive emission should be considered.

What mechanisms could be involved in the pathogenesis of mortality induced by NO_x? Previous studies reported that exposure to nitrogen oxides predisposes children to respiratory infections (Melia *et al.*, 1980; Speizer *et al.*, 1980). Short-term studies with experimental animals have also demonstrated interference with the efficiency of mucociliary clearance (Wolff, 1986) and immunologic defenses (Schnizelein *et al.*, 1980). All of the foregoing evidence points to the fact that NO_x increases susceptibility to respiratory infections and thus may conceivably increase mortality due to respiratory diseases in the exposed population.

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REFERENCES

Anscombe, F. J. (1948). The transformation of Poisson binomial and negative binomial. *Biometrika* **35**, 246–254.

Böhm, G. M., Saldiva, P. H. N., Pasqualucci, C. A. G., Massad, E., Martins, M. A., Zin, W. A., Cardoso, W. V., Criado, P. M. P., Komatsuzaki, M., Sakae, R. S., Negri, E. M. M., Lemos, M., Capelozzi, V. D., Crestana, C., and Silva, R. (1989). Biological effects of air pollution in São Paulo and Cubatão. *Environ. Res.* **49**, 208–216.

CETESB (1991). "Relatório de Qualidade do ar na Região Metropolitana de São Paulo e em Cubatão—1990." [In Portuguese]

Dockery, D. W., Speizer, F. E., Stram, D. O., Ware, J. H., and Spengler, J. D. (1989). Effects of inhable particles on respiratory health of children. *Am. Rev. Respir. Dis.* **139**, 587–594.

Fairley, D. (1990). The relationship of daily mortality to suspended particulates in Santa Clara County 1980–1986. *Environ. Health Perspect.* **89**, 159–168.

Firket, M. (1936). Fog among the Meuse Valley. *Trans. Faraday Soc.* **32**, 1192–1197.

Her Majesty's Public Health Service (1954). "Mortality and Morbidity during the London Fog of December 1952." *Public Health and Medical Subjects Report No. 95.* Her Majesty's Stationary Office.

Massad, E., Saldiva, P. H. N., Caldeira, M. P. R., Cardoso, L. M. N., Moraes, A. M., Calheiros, D. F., Silva, R,. and Böhm, G. M. (1986). Toxicity of prolonged exposure to ethanol and gasoline auto-engine exhaust. *Environ. Res.* **40**, 479–486.

Mazumdar, S., Schimmel, S., and Higgins, I. T. T. (1982). Relation of daily mortality to air pollution: An analysis of 14 London winters, 1958/59–1971/72. *Arch. Environ. Health* **37**, 213–220.

Melia, R. J. W., Florey, C. D. V., Chinn, S., Goldstein, B. D., Brooks, A. G. F., John, H. H., Clark, D., Craighead, I. B., and Webster, X. (1980). The relationship between indoor air pollution from nitrogen dioxide and respiratory illness in primary schoolchildren. *Bull. Physiopathol. Respir.* **16**, 7–8.

Pope, C. A., III, Schwartz, J., and Ranson, M. R. (1992). Daily mortality and PM_{10} pollution in Utah Valley. *Arch. Environ. Health* **47**, 211–217.

Saldiva, P. H. N., King, M., Delmonte, V. L. C., Macchione, M., Parada, M. A. C., Daliberto, M. L., Sakae, R. S., Criado, P. M. P., Silveira, P. L. P., Zin, W. A., and Böm, G. M. (1992). Respiratory alterations due to urban air pollution: an experimental study in rats. *Environ. Res.* **57**, 19–33.

Schimmel, H. (1978). Evidence for possible acute health effects of ambient air pollution from time series analysis: Methodological questions and some new results based on New York City daily mortality. *Bull. N. Y. Acad. Med.* **54**, 1052–1108.

Schnizelein, C. T., Bice, D. E., Rebar, A. H., Wolf, R. K., and Beethe, R. L. (1980). Effect of lung damage by acute exposure to nitrogen dioxide on lung immunity in the rat. *Environ. Res.* **23**, 362–370.

Schwartz, J., and Marcus, A. (1990). Mortality and air pollution in London: A time series analysis. *Am. J. Epidemiol.* **131**, 185–194.

Schwartz, J. (1991). Particulate air pollution and daily mortality in Detroit. *Environ. Res.* **56**, 204–213.

Schwartz, J., and Dockery, D. W. (1992a). Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am. Rev. Respir. Dis.* **145**, 600–604.

Schwartz, J., and Dockery, D. W. (1992b). Particulate air pollution and daily mortality in Steubenville, Ohio. *Am. J. Epidemiol.* **135**, 12–19.

Speizer, F. E., Ferris, B. G., Jr., Bishop, Y. M. M., and Spengler, J. (1980). Respiratory rates and pulmonary function in children associated with NO_2 exposure. *Am. Rev. Respir. Dis.* **121**, 3–10.

U.S. EPA (1982). "Air Quality Criteria for Particulate Matter and Sulfur Oxides." Office of Research and Development, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Wichmann, H. E., Mueller, W., Althoff, P., Beckmann, M., Bocter, N., Csicsaky, M. J., Jung, M., Molik, B., and Schoenberg, G. (1989). Health effects during a smog episode in West Germany in 1985. *Environ. Health Perspect.* **79**, 89–99.

Wolff, R. K. (1986). Effects of airborne pollutants on mucociliary clearance. *Environ. Health Perspect.* **66**, 223–227.