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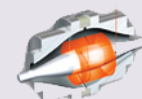
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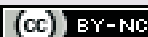
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Association of sulfur dioxide exposure with circulatory system deaths in a medium-sized city in Brazil

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Abstract

There is a demonstrable association between exposure to air pollutants and deaths due to cardiovascular diseases. The objective of this study was to estimate the effects of exposure to sulfur dioxide on mortality due to circulatory diseases in individuals 50 years of age or older residing in São José dos Campos, SP. This was a time-series ecological study for the years 2003 to 2007 using information on deaths due to circulatory disease obtained from Datasus reports. Data on daily levels of pollutants, particulate matter, sulfur dioxide (SO₂), ozone, temperature, and humidity were obtained from the São Paulo State Environmental Agency. Moving average models for 2 to 7 days were calculated by Poisson regression using the R software. Exposure to SO₂ was analyzed using a unipollutant, bipollutant or multipollutant model adjusted for mean temperature and humidity. The relative risks with 95%CI were obtained and the percent decrease in risk was calculated. There were 1928 deaths with a daily mean (\pm SD) of 1.05 \pm 1.03 (range: 0-6). Exposure to SO₂ was significantly associated with mortality due to circulatory disease: RR = 1.04 (95%CI = 1.01 to 1.06) in the 7-day moving average, after adjusting for ozone. There was an 8.5% decrease in risk in the multipollutant model, proportional to a decrease of SO₂ concentrations. The results of this study suggest that residents of medium-sized Brazilian cities with characteristics similar to those of São José dos Campos probably have health problems due to exposure to air pollutants.

Key words: Air pollution; Sulfur dioxide; Cardiovascular diseases; Mortality; Air pollutants; Stroke

Introduction

Circulatory diseases are the leading cause of death in Brazil and are responsible for remarkable financial and social costs, as observed in the State of São Paulo, where R\$500 million (US\$1 = ~R\$1.70) were spent in hospitalization of individuals aged 50 years or more in 2010 due to these causes (1). Numerous risk factors for circulatory diseases have been well elucidated, such as age, diabetes, dyslipidemia, smoking, alcoholism and, more recently, exposure to environmental factors such as air pollution (2,3).

Environmental pollution is an important topic today because it is a preventable public health problem. Its principal sources of emissions are the industries and combustion motor vehicles and the main air pollutants are particulate matter (PM₁₀), sulfur dioxide (SO₂), ozone (O₃), carbon monoxide (CO), and nitrogen oxides (NO_x) (4). It has been shown that, even when within acceptable standards according to environmental legislation, exposure to pollutants is a

risk factor for both cardiovascular and respiratory morbidity and mortality (5-8).

It is known that the impact of pollutants on vascular diseases is greater among adult and the elderly, while respiratory diseases are more common among children and the elderly (9).

Moreover, the adverse effects of exposure to air pollutants occur both in populations living in large cities and in medium-sized cities (10-12).

Study areas in São Paulo have shown an association between exposure and hospital admissions for acute myocardial infarction, showing a stronger association with SO₂ (10). A European study (APHEA-II) suggested that SO₂ can have an independent role in triggering cardiovascular events and hospitalizations due to these causes, coinciding significantly with increases in daily levels of SO₂ on the same day and on the day before exposure (13).

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Are the effects of exposure to SO₂ the same in medium-sized cities? Faced with this challenge, the aim of this study was to estimate these effects on mortality due to circulatory disease in São José dos Campos, SP, Brazil.

Material and Methods

This was an ecological time-series study in which information on deaths from circulatory disease was obtained for individuals 50 years of age or older. The study was conducted in São José dos Campos, a medium-sized city located 80 km from São Paulo, between two mountain ranges, with a population of about 700,000 inhabitants. The city is located at latitude 23° 11' S and longitude 45° 53' W and its altitude is 600 m above sea level. It has about 1100 industrial establishments with emphasis on automobile manufacturing, aerospace and pharmaceutical industries, and oil refinery. The city is crossed by the Dutra Highway, which is the most important highway in Brazil with heavy car, truck and bus traffic involving about 130,000 vehicles per day (14).

Data about the selected circulatory diseases culminating in death were obtained from the Brazilian Mortality Information System (SIM). According to the International Classification of Diseases, 10th revision, they were coded as ICD-10 = I10, I11, I15, and I20 to I25 (heart diseases), and I60 to I67 (stroke). The study considered the data for the period from January 1, 2003 to December 31, 2007.

We obtained data about the daily levels of air pollutants such as SO₂, PM₁₀ and O₃ from the São Paulo State Environmental Agency (CETESB), which has a monitoring station in the central region of São José dos Campos located 2 km north of the Dutra Highway. Data collection about the levels of pollutants was started at the first hour of the day and continued for 24 h. All data were quantified in µg/m³, considering the daily average for SO₂ and PM₁₀ and a maximum of 1 h of the day for O₃.

In São José dos Campos, the PM₁₀ pollutant is composed of nitrate, sulfate and chloride anions and constituent particles of soil and soot; sulfate was predominantly found in the fine fraction (PM_{≤2.5}), the lowest values were detected for percent chloride ion, which was the predominant coarse fraction (PM_{2.5-10}); for nitrate, the largest percentages were found in the coarse fraction (PM_{2.5-10}), approximately two times higher than those found in the PM_{≤2.5} (15).

Temperature and relative humidity data were obtained from the Foundation for Science, Technology and Space Applications (FUNCATE).

The dependent variable was death due to circulatory diseases; the independent variable was sulfur dioxide, adjusted for PM₁₀, O₃, mean temperature and humidity.

Since the manifestations of exposure to pollutants are believed to present a lag effect, i.e., that an individual exposed to pollution today may present health problem on the same day or some days later, models with moving average ranging

from 2 to 7 days after exposure to the air pollutant were constructed. The moving average, in turn, is a tool used to obtain the cumulative effect of concentrations of pollutants and is more consistent with reality. Studies do not show consensus about the days included in the moving average (16).

Statistical analysis

Time-series analysis was used, with the unit of observation being the day and not the individual. The analysis assessed the fraction of the daily variations in death counts that was explained by the daily variations in air pollution, SO₂ in particular, of the preceding days, after controlling for the other variables that varied in time. We used generalized linear models of Poisson regression to estimate the association between exposure to SO₂ and deaths due to circulatory system conditions in persons aged 50 years or more, using the R software (R Systems International, India). We chose this statistic approach because the unit of study, death due to circulatory disease, is a counting event.

The analysis was based on a unipollutant model for SO₂ adjusted for average temperature and humidity. Bipollutant models were constructed, a model with SO₂ and PM₁₀ and the other with SO₂ and O₃. The multipollutant model included SO₂, particulate matter and ozone adjusted for temperature and humidity. Relative risks (RR) were estimated for diseases of the circulatory system, for heart disease and stroke.

Thus, we obtained the coefficients (coeff) and its standard deviations (SD) that permitted the calculation of RR and 95% confidence intervals (95%CI), through the formulas: RR = exp (coeff) and 95%CI = exp [coeff ± 1.96 (SD)].

We report descriptive analysis of all study variables and correlations among them through Pearson's correlation coefficients, for which we used the computer program SPSS version 15.0. The decrease in risk of death for the interquartile difference for SO₂ was estimated using the formula: PD = [exp (-coeff * VIQPOL) - 1] * 100, where PD is the percent decrease in the risk of circulatory deaths and VIQPOL is the difference between the values of the first and third quartiles of the concentration of this pollutant. PD was estimated only for SO₂, considering the difference between the values of the first and third quartiles of the concentration of this pollutant obtained by the multipollutant model for circulatory diseases. The level of significance was set at 5% for all tests.

Results

A total of 10,111 deaths of individuals aged 50 years or more occurred during the study period from January 1, 2003 to December 31, 2007; 1928 of these deaths (19.1%) were due to circulatory diseases. There were 1021 (53.0%) deaths due to cardiovascular diseases and 907 (47.0%) deaths due to stroke. The descriptive analysis of the variables under study is given in Table 1. The average particulate matter was

Table 1. Daily mean values of the variables studied in São José dos Campos, Brazil, 2003-2007.

	Mean \pm SD	Minimum	Maximum
Deaths	1.06 \pm 1.03	0	6
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	26.97 \pm 14.8	4	100
SO ₂ ($\mu\text{g}/\text{m}^3$)	4.38 \pm 3.52	1	34
O ₃ ($\mu\text{g}/\text{m}^3$)	80.00 \pm 33.3	5	232
Temperature ($^{\circ}\text{C}$)	21.73 \pm 3.84	12.7	36.2
Humidity (%)	76.24 \pm 15.0	33	100.0

PM₁₀ = particulate matter.

26.9 \pm 14.8 $\mu\text{g}/\text{m}^3$, not exceeding the established pattern of 50 $\mu\text{g}/\text{m}^3$ annual average or the average annual daily average of 150 $\mu\text{g}/\text{m}^3$. Annual average daily level of SO₂ was 4.4 \pm 3.5 $\mu\text{g}/\text{m}^3$ and a maximum of 1 h of the day for O₃ was 232 \pm 33.3 $\mu\text{g}/\text{m}^3$, with acceptable values for the two pollutants having been established up to 80 and 160 $\mu\text{g}/\text{m}^3$, respectively. This shows that SO₂ did not exceed the acceptable value, whereas O₃ exceeded this limit on 34 occasions for a total of 1826 days of study.

The year-by-year variation during the study period is shown in Figure 1. There was a high seasonal behavior for PM and SO₂, but not for O₃.

The mortality rate from all circulatory diseases varied little in terms of total annual number, with the lowest number occurring in 2005 (366 deaths) and the largest in 2007 (401 deaths). However, when the rate was analyzed on a monthly basis there was seasonal variation, with larger numbers in the colder months of the year and lower numbers in warmer months.

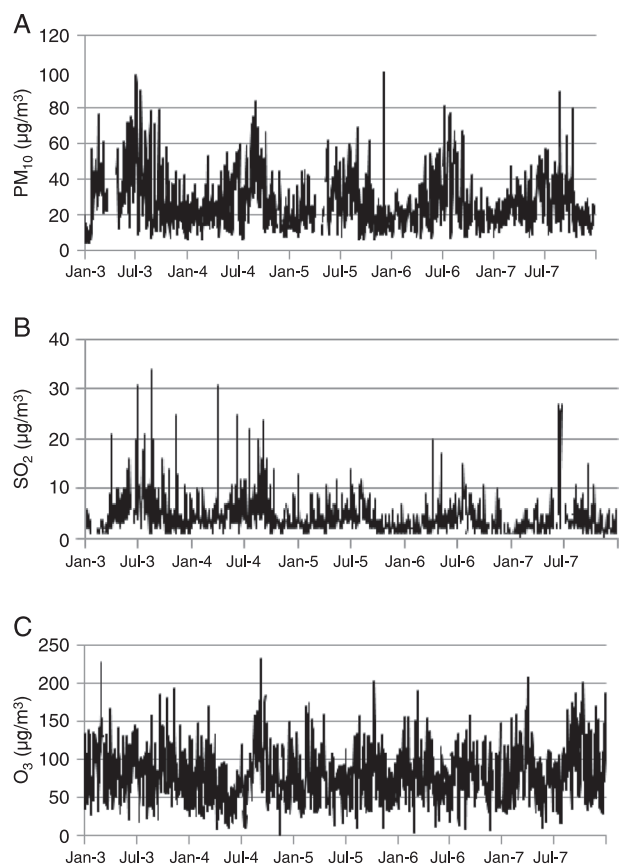
Table 2 presents the correlation matrix between the variables of the study. We observed positive correlations between pollutants, whereas deaths due to circulatory diseases showed a positive correlation with PM₁₀ and SO₂, and a negative correlation with O₃. The weather variables showed negative correlations with deaths and air pollution, except for temperature, which was positively correlated with PM₁₀ and O₃.

A generalized linear model using Poisson regression analysis was used to determine the association between exposure to SO₂ and deaths due to circulatory diseases and is expressed as RR (Figure 2A-D). The model presents the RR and their 95%CI for SO₂ in the unipollutant model, in the bipollutant model and in the multipollutant model with PM and O₃, adjusted for mean temperature and humidity. The RR for death due to circulatory diseases, heart diseases and stroke are shown in Table 3; it is possible to note the contribution of death due to stroke to mortality due to circulatory diseases. The maximum RR obtained was 1.04 (95%CI = 1.01 to 1.06) for the bipollutant model adjusted for O₃. There was a decreased risk of death of approximately 8.5% for the fifth, sixth, and seventh moving average, in the multipollutant model for a decrease in the interquartile

Table 2. Pearson's correlation matrix between all atmospheric variables. São José dos Campos, Brazil, 2003-2007.

	Deaths	PM ₁₀	SO ₂	O ₃	Temperature	Humidity
Deaths	1	0.05*	0.06*	-0.02	-0.04	-0.01
PM ₁₀		1	0.51*	0.39*	0.16*	-0.37*
SO ₂			1	0.26*	-0.03	-0.30*
O ₃				1	0.04*	-0.35*
Temperature					1	-0.68*
Humidity						1

PM₁₀ = particulate matter. *P < 0.05.

**Figure 1.** Daily pollutant concentration during the study period. São José dos Campos, Brazil, 2003-2007. A, PM₁₀; B, SO₂; C, O₃.

difference (3 $\mu\text{g}/\text{m}^3$) of SO₂ (Figure 2E).

Discussion

This is the first time-series study reported to estimate the association between exposure to air pollutants and circulatory deaths in a medium-size city in Brazil.

This was an ecological study, since the unit of study was the population and not the individual. The choice of statistical analysis using a generalized linear model rather

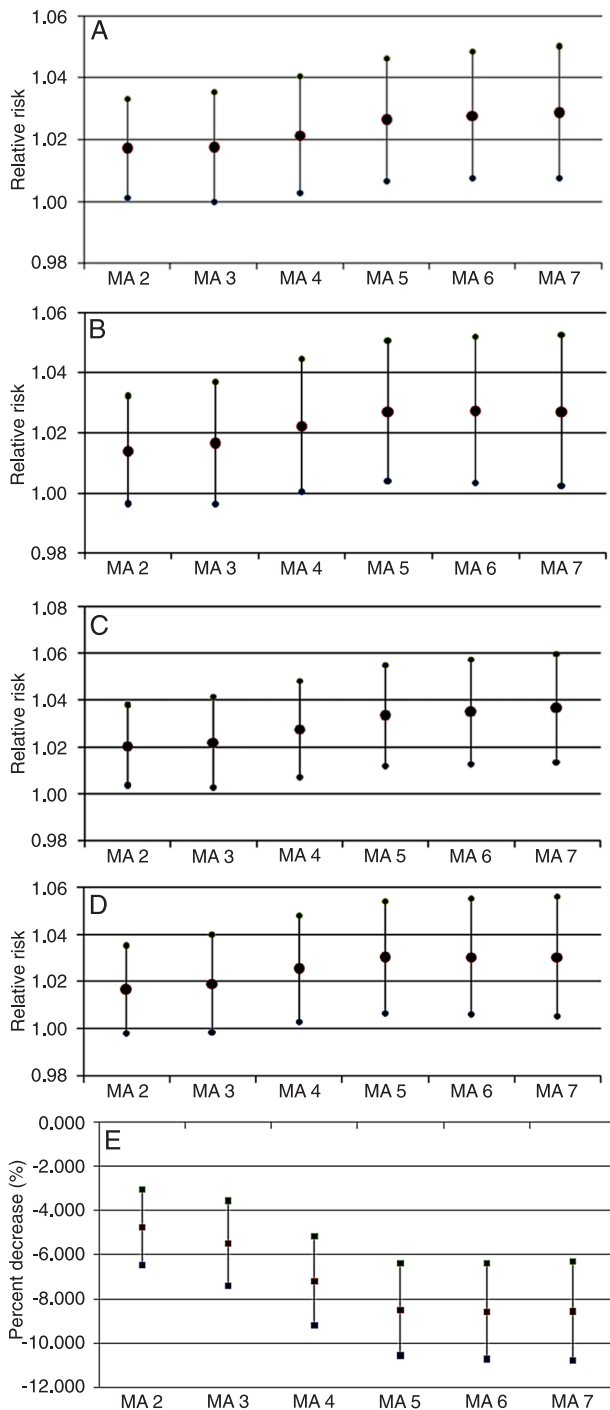


Figure 2. Relative risks and 95% confidence interval for deaths due to cardiovascular circulatory diseases by exposure to sulfur dioxide: *A*, unipollutant model; *B*, bipollutant model adjusted for PM_{10} ; *C*, bipollutant model adjusted for O_3 ; *D*, multipollutant model adjusted for PM_{10} and O_3 ; *E*, percent decrease in risk according to the interquartile difference ($3 \mu g/m^3$) of SO_2 in the multipollutant model according to moving average of two days (MA 2) up to 7 days (MA 7). São José dos Campos, SP, 2003-2000.

Table 3. Relative risk (RR) and respective 95% confidence interval (95%CI) for deaths due to circulatory diseases, cardiac diseases and stroke in relation to exposure to sulfur dioxide in a multipollutant model. São José dos Campos, Brazil, 2003-2007.

	Circulatory diseases [RR (95%CI)]	Cardiac diseases [RR (95%CI)]	Stroke [RR (95%CI)]
MA 2	1.016 (0.998-1.035)	1.011 (0.986-1.037)	1.022 (0.996-1.048)
MA 3	1.019 (0.998-1.040)	1.011 (0.982-1.040)	1.025 (0.995-1.055)
MA 4	1.025 (1.003-1.048)	1.020 (0.990-1.052)	1.027 (0.995-1.059)
MA 5	1.030 (1.007-1.054)	1.025 (0.993-1.058)	1.031 (0.997-1.066)
MA 6	1.030 (1.006-1.055)	1.021 (0.993-1.056)	1.035 (1.000-1.072)
MA 7	1.030 (1.005-1.056)	1.019 (0.985-1.055)	1.036 (1.000-1.074)

MA = moving average. $P < 0.05$ for the values in bold (Poisson regression).

than a generalized additive model was based on a study conducted by Conceição et al. (17), which demonstrated that both models yield consistent results, without compromising the end result of the study. The generalized linear model was also used successfully by Arbex et al. (18) to assess the association between exposure to total suspended particles resulting from biomass burning and hospitalizations for hypertension.

The levels of pollutants reported in the present study differ from those reported for others, such as a study conducted in São Paulo, the Brazilian metropolis, which demonstrated 24-h PM_{10} values exceeding by several times the limit value of $150 \mu g/m^3$ (19). This finding is consistent, since São José dos Campos is a medium-sized city with a smaller vehicle fleet (230,000 vehicles versus 5 million in São Paulo) and industrial park, which are mainly responsible for the emission of PM_{10} (20). Also in São Paulo, the average SO_2 value was $17.71 \mu g/m^3$, which is well above the average found in the present study ($4.4 \mu g/m^3$), and O_3 levels were close to those detected in the present study ($80 \mu g/m^3$), with an average of $71.79 \mu g/m^3$ average (6).

Both environmental pollutants and the sum of monthly deaths throughout the study period showed markedly seasonal behavior, with increased levels of pollutants and number of deaths in the cooler times of the year (months of May, June and July) and decreased values in the warmer months of the year. This can be explained by the thermal inversion that occurs during the cold months, reducing the dispersion of air pollutants. Ozone, on the other hand, showed no seasonal pattern, since it is known that it is the result of chemical reactions involving sunlight, nitrogen oxides, and hydrocarbons derived primarily from vehicle emissions, unlike the mechanism of the other three pollutants.

The mechanisms involved in the genesis of circulatory diseases by exposure to pollutants have not been well explored, but a possible mechanism could be the increase in plasma fibrinogen and inflammatory factors, which lead

to increased blood viscosity, resulting in clinical cardiovascular events (21).

In particular, SO₂ resulting from the burning of fossil fuels is a major component of air pollution in many parts of the world. In urban areas, SO₂ originates from domestic heating, power generation through thermal power plants and motor vehicles. Its inhalation is responsible for adverse health effects due to its absorption by the mucous membranes of the respiratory tract (22). A study conducted by Tunnicliffe et al. (23) using electrocardiograms suggested that exposure to SO₂ can influence the autonomic nervous system, contributing to the explanation of the mechanisms involved in the cardiovascular and bronchial constriction produced by this pollutant. Another study also suggested a direct effect on the autonomic nervous system rather than effects secondary to a systemic inflammatory response, having found that short-term exposure to SO₂ causes a decrease in cardiac vagal control measures (24).

In the present study, we demonstrated the association of exposure to SO₂ and circulatory events that result in death. Exposure to SO₂ was significantly associated with mortality due to circulatory diseases (maximum RR in the moving average of 7 days = 1.036; 95%CI = 1.014-1.060), after adjusting for O₃. Although the RR estimated in this study were of low magnitude, it is important to note that exposure to air pollutants is a frequent event, resulting in a marked impact on the health system and the exposed individual.

In another study carried out in São Paulo, an increase of 10 µg/m³ in SO₂ concentrations led to an 11% increase in the risk of hospital admissions due to respiratory disease, a 3% increase in hospital admissions due to cardiovascular diseases, and a 7% increase in hospital admissions due to ischemic heart disease in elderly people (18).

Along this line, Sunyer et al. (13) found in seven European regions a significant increase in the daily numbers of all cardiovascular admissions except for stroke, particularly ischemic heart disease (IHD), with an increase in the levels of SO₂ in the same day and the day before. After adjustment for PM₁₀, the combination of SO₂ with IHD admissions remained significant among individuals younger than 65 years, but not among individuals older than 65 years. An increase of 10 µg/m³ of SO₂ in the daily average corresponded to 0.7% of all cardiovascular hospitalizations on the same day and the next. On the other hand, a study conducted in Finland identified an association between exposure to PM and death from stroke (25)

In the present study, we chose to estimate the decrease in RR for a decrease in the interquartile difference in SO₂ (3 µg/m³); under these conditions there was a decreased

risk of death reaching a maximum value of approximately 8.5% in the multipollutant model. This finding reinforces the need to implement measures to decrease the concentrations of air pollutants.

This study may have limitations where the individual exposures are not considered, taking as the basis a homogeneous atmosphere throughout the analysis. Therefore, we cannot say that an individual who died was necessarily exposed to higher pollution levels. The use of the generalized linear model instead of a generalized additive model may have been another limitation, because the general additive model is a more parsimonious model that requires a smaller number of explanatory variables. Another limitation may have been a mistake in the coding of cause of death, besides the lack of information on comorbidities. The database used in this study does not identify whether the subject is a smoker or non-smoker. Another limitation was the lack of separation between deaths due to heart disease and deaths due to stroke. In our study, stroke made the most expressive contribution to the deaths recorded.

We should be careful regarding the exclusive involvement of SO₂ in the occurrence of deaths because other pollutants such as CO, NO and NO₂ were not included due to the fact that they are not estimated by CETESB. It is important to note that this statistical approach and this type of study may suggest a relationship, but not necessarily a causal effect. However, it serves as a basis for the management of public health, social and financial aspects of the country.

The results of this study suggest that residents of medium-sized Brazilian cities with characteristics similar to those of São José dos Campos, which is crossed by a highway with considerable truck and bus traffic, and having a similar industrial complex, may also be affected by exposure to environmental pollutants, even when they are present in low concentrations and within the limits acceptable by environmental legislation (26).

Moreover, the death outcome examined in this study, although being the most serious, is just one of the outcomes of exposure to air pollutants, also represented by emergency consultations, hospitalizations and poorer quality of life. Thus, we observed an important role of SO₂ when combined with the risk of circulatory deaths in the elderly in a Brazilian medium-sized city.

Acknowledgments

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