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# The effects of air pollution on cardiovascular diseases: lag structures

# Efeitos da poluição do ar nas doenças cardiovasculares: estruturas de defasagem

## ABSTRACT

**OBJECTIVE**: To assess the lag structure between air pollution exposure and elderly cardiovascular diseases hospital admissions, by gender.

**METHODS**: Health data of people aged 64 years or older was stratified by gender in São Paulo city, Southeastern Brazil, from 1996 to 2001. Daily levels of air pollutants (CO, $PM_{10}$, $O_3$, $NO_2$, and $SO_2$) , minimum temperature, and relative humidity were also analyzed. It were fitted generalized additive Poisson regressions and used constrained distributed lag models adjusted for long time trend, weekdays, weather and holidays to assess the lagged effects of air pollutants on hospital admissions up to 20 days after exposure.

**RESULTS**: Interquartile range increases in $PM_{10}$ (26.21 μg/m$^3$) and $SO_2$ (10.73 μg/m$^3$) were associated with 3.17% (95% CI: 2.09-4.25) increase in congestive heart failure and 0.89% (95% CI: 0.18-1.61) increase in total cardiovascular diseases at lag 0, respectively. Effects were higher among female group for most of the analyzed outcomes. Effects of air pollutants for different outcomes and gender groups were predominately acute and some "harvesting" were found.

**CONCLUSIONS**: The results show that cardiovascular diseases in São Paulo are strongly affected by air pollution.

**KEYWORDS: Cardiovascular diseases, epidemiology. Air pollution, adverse effects. Air pollution, analysis. Gender. Hospital records. Time series studies.**

## RESUMO

**OBJETIVO**: Investigar a estrutura de defasagem entre exposição à poluição do ar e internações hospitalares por doenças cardiovasculares em idosos, separada por gênero.

**MÉTODOS**: Os dados de saúde de pessoas com mais de 64 anos de idade foram estratificados por gênero, na cidade de São Paulo, entre 1996 e 2001. Os níveis diários de poluentes do ar (CO, $PM_{10}$, $O_3$, $NO_2$, $SO_2$) e os dados de temperatura mínima e umidade relativa do ar foram também foram analisados. Foram utilizados modelos restritos de distribuição polinomial em modelos aditivos generalizados de regressão de Poisson para estimar os efeitos dos poluentes no dia da exposição e até 20 dias após, controlando-se para sazonalidades de longa e curta durações, feriados e fatores meteorológicos.

**RESULTADOS**: Variações interquartis de $PM_{10}$ (26,21 μg/m$^3$) e $SO_2$ (10,73 μg/m$^3$)

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foram associados com aumentos de 3,17% (IC 95%: 2,09-4,25) nas admissões por insuficiência cardíaca congestiva e de 0,89% (IC 95%: 0,18-1,61) para admissões por todas as doenças cardiovasculares no dia da exposição, respectivamente. Os efeitos foram predominantemente agudos e maiores para o gênero feminino. Além disso, foi observado efeito colheita.

**CONCLUSÕES**: Os achados mostraram que as doenças cardiovasculares em São Paulo são fortemente afetadas pela poluição do ar.

**DESCRITORES: Doenças cardiovasculares, epidemiologia. Poluição do ar, efeitos adversos. Poluição do ar, análise. Gênero. Registros hospitalares. Estudos de séries temporais.**

## INTRODUCTION

The acute effects of air pollutants on respiratory and cardiovascular morbidity and mortality are well known.[2,9-13] Also, although the relative effects of air pollutants are larger for respiratory events than for cardiovascular diseases, the numbers of adverse health outcomes attributable to air pollutants are much larger for cardiovascular than for respiratory causes.[1,6] For cardiovascular diseases, the elderly people are those who present the highest susceptibility.[1]

The lag structure between air pollutants exposure and effects are matter of concern. Braga et al[3] reported short-term lag structures between $PM_{10}$ exposure and deaths to cardiovascular diseases and myocardium infarction in 10 US cities, controlling for weather confounding. Compared to respiratory diseases, cardiovascular effects due to $PM_{10}$ were found to be more acute with adverse responses seen at the same day or, at the most, on the subsequent day. Recently, investigating the effects of $PM_{10}$ on cardiovascular diseases deaths in European cities, Zanobetti et al[16] used a longer distributed lag model, from day zero to day 40, and showed a five-time higher effect than that estimated for the day and day after exposures only. It is highly relevant for estimates of air pollution attributed adverse effects on health. In São Paulo, studies have focused on very short time lagged effect estimates with, at most, a week exposure time period. In a recent panel study, Santos et al[14] showed acute effects of $SO_2$ and CO on blood pressure and heart rate variability in healthy people with a short-time lag structure.

Other issue that has been insufficiently addressed in environmental epidemiology studies of air pollution on health is the potential difference of susceptibility by gender.

The present study aimed at investigating the lag structure of the effects of daily criteria air pollutants levels on morbidity, using the daily number of hospital admissions due to total cardiovascular disease, ischemic heart disease and congestive heart failure.

## METHODS

Daily records of hospital admissions due to cardiovascular diseases (ICD-10: I00-I99) in people older than 64 years of age in São Paulo, Southeastern Brazil, were obtained from the *Departamento de Informação e Informática do Sistema Único de Saúde* (Datasus - Department of Data Analysis of the Unified Health System) from June 1996 to November 2001. Three outcomes of interest were defined and stratified by gender: all cardiovascular diseases, congestive heart failure (I50), and ischemic heart disease (I20-I25).

Daily records of carbon monoxide, particulate matter with an aerodynamic profile ≤10 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$) and ozone ($O_3$) were obtained from *Companhia de Tecnologia de Saneamento Ambiental de São Paulo* (Cetesb - State Sanitary Agency) for the same period. There were 14 monitoring stations spread all over the city, although not all of them measure all pollutants. It was adopted the average of all stations that measured each pollutant as a citywide exposure status. The measurement adopted for carbon monoxide was the highest 8-hour moving average in seven stations; $NO_2$ and $O_3$ concentrations were computed as the highest hourly average in seven and six stations, respectively; and for $PM_{10}$ (14 stations) and $SO_2$ (6 stations) were adopted 24-hour averages. All pollutants were measured in the period from 1:00 am to 12:00 pm.

Daily minimum temperature and daily mean of relative humidity were obtained from the *Instituto de Astronomia e Geofísica* (IAG - Institute of Astronomy and Geophysics) of the Universidade de São Paulo.

Generalized additive Poisson regressions were fitted to the logarithm of the expected value of elderly car-

diovascular hospital admissions in each outcome and gender subsets as the sum of smooth and linear functions of the predictor variables. The nonparametric function adopted was LOESS, a moving regression smoother. In order to assure convergence of its iterative estimation procedure providing biased estimates of regression coefficients and standard errors when non-parametric functions are adopted,[7] it was used more stringent convergence parameters than the default settings of S-Plus software. Besides, it was adopted LOESS smoother to only one parameter (time trend) which minimizes estimates errors.

Outcome and gender-specific smooth parameters for time were chosen to remove long-term trends from the data, removing seasonality, and minimizing autocorrelation of residuals. Each admission is an independent event, and autocorrelation of residuals indicates that there are omitted time-dependent covariates whose variation may confound air pollution associations. If the autocorrelation is removed, the remaining variation from omitted covariates has no systematic temporal pattern, and hence confounding is less likely. When necessary, autoregressive terms were incorporated to eliminate serial correlation from the residuals.

Indicators for weekdays and holidays were included in the models. In order to reduce sensitivity to outliers in the dependent variable it was used robust regression (M-estimation).

Air pollution and weather variables as temperature and humidity can induce health effects not only on the same day of the exposure but also on subsequent days. Hence the number of admissions on a given day will depend on the same day effect of that day's pollution/weather, but also on the lagged effect of the previous day's pollution/weather. Different approaches have been tried in order to estimate the contribution of each day of exposure on the endpoint. The lag structures between air pollution and health have been analyzed using different approaches[2-5,9,16] and time lags.

An unrestricted distributed lag model shows:

$$\text{Log}\,(E(Y)) = \alpha + \text{covariates} + \beta_0 X_t + \ldots + \beta_q X_{t-q} + \varepsilon_t \quad (1)$$

where Y is the daily count of admissions, E(Y) is the expected value of that count, and $X_{t-q}$ is the pollutant/weather concentration q days before the admissions. In this analysis it was adopted a constrained lag structure, i.e. a polynomial distributed lag model. Usually applied to social sciences studies and econometrics, the use of this approach in epidemiology has been described in air pollution time series.[3,16] In this study, it was investigated the lag structure of air pollution and weather effects on cardiovascular hospital admissions using a third degree polynomial with 21 days, from lag zero to lag 20, which imposes constraints, but gives enough flexibility to estimate a biologically plausible lag structure, and controlling multicollinearity better than an unconstrained lag model. The standard errors of the estimates for each day were adjusted for overdispersion. Air pollutants effects were presented as percentage increase in hospital admissions and 95% confidence intervals.

Co-pollutant or multi-pollutant models were not used because the inclusion of a third degree polynomial highly correlated with the others already in the model

**Table 1** - Descriptive analyses of cardiovascular diseases hospital admissions, air pollutants and weather variables. São Paulo, Brazil, 1996-2001.

| Variable | Daily Mean | SD | Minimum | IQR | Maximum |
|---|---|---|---|---|---|
| Cardiovascular | | | | | |
| Total | 43.43 | 15.69 | 9 | 21 | 163 |
| Female | 22.04 | 8.77 | 3 | 11 | 93 |
| Male | 21.39 | 8.42 | 3 | 12 | 72 |
| Congestive heart failure | | | | | |
| Total | 10.46 | 4.28 | 0 | 6 | 27 |
| Female | 5.82 | 2.87 | 0 | 3 | 19 |
| Male | 4.64 | 2.56 | 0 | 3 | 16 |
| Ischemic heart disease | | | | | |
| Total | 10.57 | 4.71 | 0 | 7 | 27 |
| Female | 4.76 | 2.70 | 0 | 3 | 14 |
| Male | 5.81 | 3.04 | 0 | 5 | 16 |
| Pollutants | | | | | |
| $PM_{10}$ (µg/m³) | 52.7 | 23.9 | 13.9 | 26.2 | 186.3 |
| $O_3$ (µg/m³) | 76. 6 | 42.8 | 10.2 | 51.2 | 389.5 |
| $SO_2$ (µg/m³) | 17.0 | 9.2 | 2.0 | 10.7 | 75.2 |
| $NO_2$ (µg/m³) | 102.7 | 47.6 | 22.2 | 54.6 | 421.6 |
| CO (ppm) | 3.1 | 1.5 | 0.5 | 1.7 | 12.6 |
| Weather | | | | | |
| Temperature* (ºC) | 15.0 | 3.5 | -0.0 | 5.4 | 23.2 |
| Humidity (%) | 80.5 | 8.3 | 45.7 | 10.4 | 96.6 |

IQR: Interquartile range
*Minimum temperature of the day

**Table 2** - Pearson correlation coefficients between air pollutants and weather variables. São Paulo, Brazil,1996-2001.

| Variable | $O_3$ | CO | $NO_2$ | $SO_2$ | $PM_{10}$ | Tmin | Hmed |
|---|---|---|---|---|---|---|---|
| $O_3$ | 1.00 | | | | | | |
| CO | -0.05* | 1.00 | | | | | |
| $NO_2$ | 0.32* | 0.67* | 1.00 | | | | |
| $SO_2$ | 0.21* | 0.57* | 0.70* | 1.00 | | | |
| $PM_{10}$ | 0.29* | 0.75* | 0.81* | 0.77* | 1.00 | | |
| Tmin | 0.08* | -0.16* | -0.20* | -0.31* | -0.31* | 1.00 | |
| Hmed | -0.31* | -0.34* | -0,36* | -0.42* | -0.51* | 0.08* | 1.00 |

Tmin: Minimum temperature; Hmed: Relative humidity
*p<0.01

could increase multicollinearity thus distorting the estimates.

Statistical analyses were carried out using S-Plus™ software, version 4.5.

## RESULTS

Table 1 presents the descriptive analyses of the variables used in the analyses. Ischemic heart disease and congestive heart failure were almost 50% of all cardiovascular diseases hospital admissions. Gender distribution did not present a well-defined pattern.

During the period of study only $PM_{10}$ (1996 and 1997) and $NO_2$ (1996, 1997, 1998, and 2001) presented means that exceeded their respective annual air quality standards (50 μg/m³ and 100 μg/m³, respectively). $O_3$ exceeded its daily standard (160 μg/m³) 72 times, CO (9 ppm) 16 times, $NO_2$ (320 μg/m³) seven times, and $PM_{10}$ (150 μg/m³) 10 times. Except for $O_3$, it was observed a declining trend in air pollution levels along the period of study. Descriptive analyses for the whole period showed that $PM_{10}$, $NO_2$ and $O_3$ reached maximum daily records well above their standards. The winter of 2000 was the coldest and the driest season during the study period. The remaining years presented very homogeneous weather records.

Table 2 presents Pearson correlation coefficients for pollutants and weather variables. Correlations between $PM_{10}$, CO, $SO_2$, and $NO_2$ were high, positive, and statistically significant, while $O_3$ correlations with them were statistically significant but lower than those observed between primary pollutants. Minimum temperature was inversely correlated with all pollutants except for $O_3$.

Figure 1 presents estimated lag structures for $SO_2$ effects on total cardiovascular diseases hospital admissions for the whole group and by gender. There is an acute effect at lag zero for whole group and at lags zero and one for the female group. No statistically significant effects were observed for the male group. There were no long-term effects in any group. $SO_2$ was chosen because it was the pollutant that presented the highest effects at lag zero. The pattern of distributed lag effects observed for the other pollutants were similar to that presented by $SO_2$, with "harvesting" observed four to seven days after the exposure.

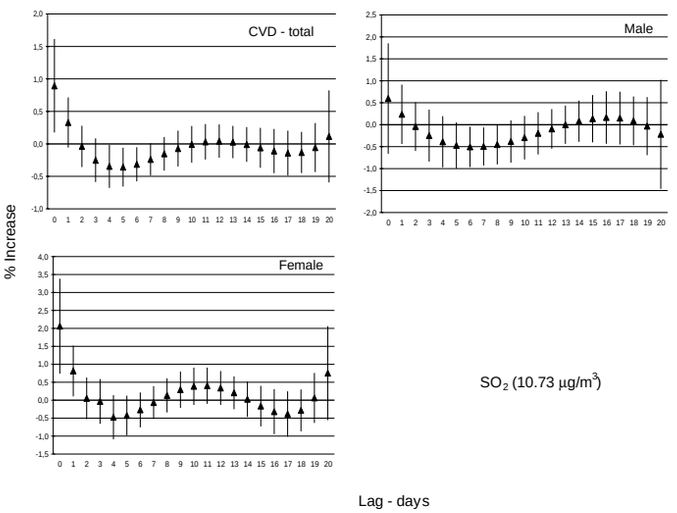


**Figure 1** - Lag structure of the effects of an interquartile range increase in $SO_2$ (10.73 μg/m³) on total, male, and female cardiovascular disease (CVD) hospital admissions. São Paulo, Brazil, 1996-2001.

For ischemic heart diseases, the estimates with $SO_2$ for the whole group showed a pattern that is similar to that observed for total cardiovascular diseases, with lags zero and one presenting statistically significant effects (Figure 2). However, in the analyses by gender it is possible to recognize two different patterns of lag structure: while for the female group the contribution of air pollution on ischemic heart diseases hospital admissions is relevant only at lags zero and one, the effect started at lag one and remained until four days after the exposure in the male group.

The effect of $PM_{10}$ on congestive heart failure hospital admissions presented a tri-phase pattern, as can be seen in Figure 3, and it is different from the other estimates previously presented. Besides the positive effects at lags

zero and one and the "harvesting" at lags five and six, there was a 10 to 12-day lagged positive effect for the whole group. This pattern is clearly driven by the $PM_{10}$ effect in the male group.

## DISCUSSION

This study was designed to assess the lag structure of air pollution on cardiovascular diseases using hospital admissions. It showed that air pollution was positively associated with cardiovascular hospital admissions and all of them presented a short-time lagged effect. Effects were higher for the female group except for congestive heart failure, which $PM_{10}$ presented a 10 to 12-day lagged positive effects in the male group.

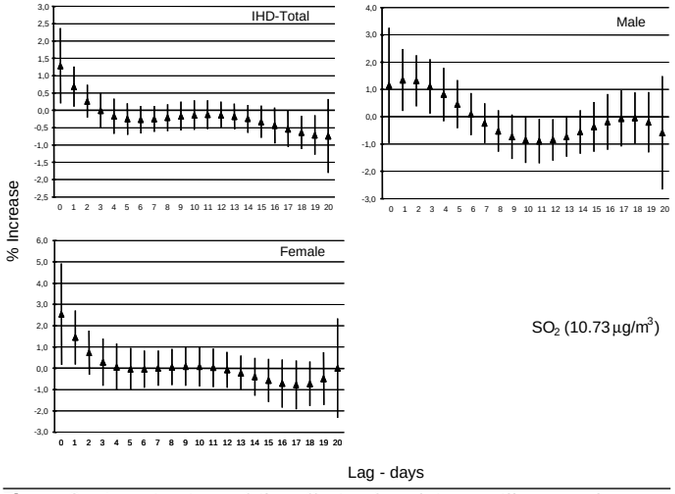


**Figure 2** - Lag structure of the effects of an interquartile range increase in $SO_2$ (10.73 µg/m³) on total, male, and female ischemic heart disease (IHD) hospital admissions. São Paulo, Brazil, 1996-2001.

It was used secondary data from different hospitals in São Paulo. Specific diagnoses on cardiac diseases may be difficult to do specially in general and/or non-university hospitals. Misclassification of ischemic heart disease cases is less likely to occur because of its characteristic clinical manifestations and severity. Also, it is usual the occurrence of arrhythmia and congestive heart failure as consequence of ischemic events and not the inverse. In fact, congestive heart failure is often a consequence of other diseases and, hence, misclassification is more plausible but still not frequent. Eventually, congestive heart failure can induce arrhythmia which may aggravate congestive heart failure. In cases like that the primary diagnosis is difficult to be defined. However, even when misclassification of congestive heart failure or arrhythmia occurs it is non-differential and hence not dependent on air pollution concentration.

It was adopted generalized additive models and LOESS smoother in the S-Plus software, a procedure that has been matter of discussion in the last two years. As pointed out by Dominici et al[7] estimates of effects and standard errors are affected in models using nonparametric functions for more than one covariate. However, in the present study, it was used LOESS smoother for controlling long-term seasonality only and it was adopted convergence parameters much more restrictive than the S-Plus version 2000 default parameters. Moreover, studies developed by these authors' group have showed that the effects of air pollution on cardiovascular diseases remained the same when estimated by generalized linear or additive models.[9]

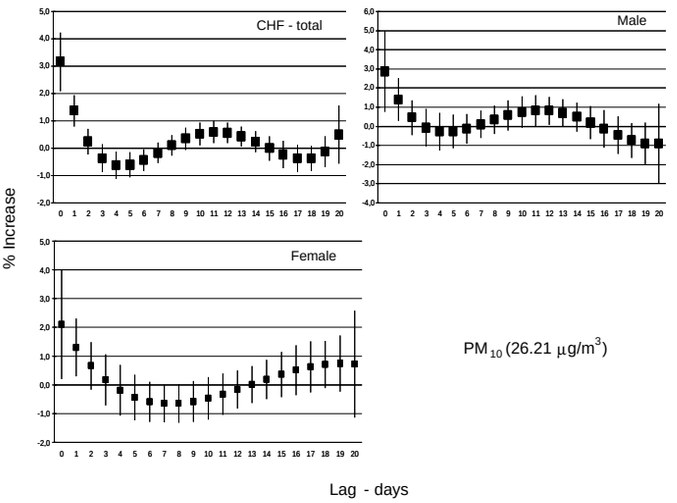


**Figure 3** - Lag structure of the effects of an interquartile range increase in $PM_{10}$ (26.21 µg/m³) on total, male, and female congestive heart failure (CHF) hospital admissions. São Paulo, Brazil, 1996-2001.

Lag structures were estimated using multivariate models controlling for confounding by seasonality adjusting for overdispersion. There were included the most probable and the most commonly used confounders in the association between air pollution or weather and cardiovascular morbidity. The great number of prolonged holidays in the middle of the week required the inclusion of a specific indicator. Even being unlikely, the possibility of incomplete adjustment for confounders always must be considered.

As pointed out in a previous study,[9] it was found an enhanced response of elderly to air pollutants. The study design does not allow speculations on health characteristics of the population analyzed in the present study but it can be assumed, due to

the age group used, that most of them could present cardiorespiratory diseases. This situation may explain the "harvesting" pattern observed for cardiovascular diseases and congestive heart failure. In this case, the exposure to air pollutants affected mainly a susceptible subgroup of the entire population, leading to a lack of subsets in the subsequent days after exposure. However, studies by Schwartz[15] and Zanobetti et al[16] carried out with using the same methodology are in agreement that the effects of air pollutants are not predominantly due to harvesting. They analyzed more than one city and this procedure controls better for collinearity effects on daily estimates of the effects that are minimized but not eliminated using constrained polynomial distributed lag models for estimates in one city only. As pointed out by Braga et al,[3] "a study in a single location risks variations in the lag structure between air pollution and daily health events that are due to sampling variability rather than related to a causal pathway". However, health, air pollution, and weather data are not available for either most of the cities in the State of São Paulo or in Brazil. The development of a national program of surveillance in air pollution health effects may provide data from different cities, which will allow estimates in more than one setting.

It is important to emphasize that acute effects were consistent across different air pollutants and diseases. It provides evidence that the study estimates are more plausible to be true and less biased.

Differently from that reported by Koken et al,[8] where male gender was identified as risk factor for cardiovascular diseases, there were found greater effects on congestive heart failure in the male group and on cardiovascular diseases and ischemic heart disease in the female group. The present study showed different results and reinforce the need for additional studies focusing on effect modification of air pollution health effects by gender.

In conclusion, the present study showed a significant association between cardiovascular diseases hospital admissions for elderly in São Paulo, and this effect varied in size by gender. The lag structure showed a very acute effect of air pollution on cardiovascular diseases and that assessing lags structures for longer periods in a single site will require additional data and statistical tools.

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