Cardiac arrhythmia emergency room visits and environmental air pollution in São Paulo, Brazil

U P Santos,[1] M Terra-Filho,[1] C A Lin,[2,3] L A A Pereira,[2,4] T C B Vieira,[2] P H N Saldiva,[2] A L F Braga[2,4,5]

[1] Pulmonary Division of Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; [2] Environmental Epidemiology Study Group, Laboratory of Experimental Air Pollution, University of São Paulo Medical School, São Paulo, Brazil; [3] Department of Internal Medicine, University of São Paulo Medical School, São Paulo, Brazil; [4] Collective Health Postgraduation Program, Catholic University of Santos, Brazil; [5] Environmental Pediatrics Program, University of Santo Amaro Medical School, São Paulo, Brazil

Correspondence to:
Alfésio Luís Ferreira Braga, Rua Francisco Octávio Pacca, 180, 4° Andar, Grajaú, São Paulo, CEP 04822-320, Brazil;
abraga@unisa.br

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ABSTRACT

Objectives: Air-pollution exposure has been associated with increased cardiovascular hospital admissions and mortality in time-series studies. We evaluated the relation between air pollutants and emergency room (ER) visits because of cardiac arrhythmia in a cardiology hospital.

Methods: In a time-series study, we evaluated the association between the emergency room visits as a result of cardiac arrhythmia and daily variations in SO_2, CO, NO_2, O_3 and PM_{10}, from January 1998 to August 1999. The cases of arrhythmia were modelled using generalised linear Poisson regression models, controlling for seasonality (short-term and long-term trend), and weather.

Results: Interquartile range increases in CO (1.5 ppm), NO_2 (49,5 $\mu g/m^3$) and PM_{10} (22.2 $\mu g/m^3$) on the concurrent day were associated with increases of 12.3% (95% CI: 7.6% to 17.2%), 10.4% (95% CI: 5.2% to 15.9%) and 6.7% (95% CI: 1.2% to 12.4%) in arrhythmia ER visits, respectively. PM_{10}, CO and NO_2 effects were dose-dependent and gaseous pollutants had thresholds. Only CO effect resisted estimates in models with more than one pollutant.

Conclusions: Our results showed that air pollutant effects on arrhythmia are predominantly acute starting at concentrations below air quality standards, and the association with CO and NO_2 suggests a relevant role for pollution caused by cars.

Air pollution is a very important issue in public health, especially in large urban centres. Estimates indicate that particulate matter (PM_{10}) inhalation is responsible for 800 000 premature deaths and 6.4 million years of life lost (YLL) worldwide.[1] In the last 15 years, a large number of epidemiological studies have shown that besides the respiratory effects of air pollution, it has been associated with acute[2–6] and chronic effects[7–10] on cardiac morbidity and mortality.

The importance of cardiovascular diseases, the primary causes of death worldwide,[11] and the large number of people exposed to air pollution have stimulated new studies, not only to better establish the exposure-response type but also to elucidate the possible mechanisms involved in the air pollution-generated adverse health effects.

The mechanisms that could possibly explain the results involve direct air pollution effects on different elements of the cardiovascular system.[12 13] Also, experimental studies in both animals and human beings[14 15] and panel studies[16–20] have shown alterations in the autonomic nervous system associated with the increase in air pollution levels. These findings brought new knowledge about pathophysiological mechanisms involved in the effects of air pollution, giving greater plausibility to the epidemiological findings.[3 21 22]

The imbalance between autonomic sympathetic and parasympathetic nervous systems is associated with a major risk of cardiac arrhythmia that could lead to an atheroma plate disruption, heart infarction and sudden death,[12 23–25] stroke[26] and heart failure.[27] These alterations could be implicated in acute effects (hours), as well as subacute effects (several hours and days) on the cardiovascular system,[12 28] associated with air pollution.

Among the cardiovascular effects, arrhythmia, a significant cause of mortality, has been associated with short-term,[4] as well as long-term,[9] exposure to air pollution, but with relatively few studies about its acute effects.[29–31]

Recent studies, using different models and methods of analysis, evaluating patients implanted with internal cardiac defibrillators, have demonstrated an association between tachyarrhythmia and gaseous pollutants and particulate matter.[32–34] Some studies carried out in Canada[35 36] also found the same association, although not statistically significant, except in a group of patients with previous electric defibrillator discharge to avoid cardiac arrhythmia.[36] These studies reported differences in the magnitude of effects, in the associated pollutant and in the lag structures, requiring better elucidations and confirmation.

On the other hand, in spite of better air quality control, the air pollution adverse health effects still persist, probably because of the non-existence of a threshold for harmful effects[37] and also because of the difficulty of reducing pollutant levels in an efficient way as a result of an increase in the number of cars in circulation in large urban centres.

The city of São Paulo, Brazil, has about 11 million inhabitants and about six million cars, and it is still growing. The objective of our study was to evaluate the relation between air pollution and emergency room visits due to tachyarrhythmia in the biggest cardiovascular specialty hospital in São Paulo, Brazil.

METHODS AND MATERIALS

Study population

This is a time-series study using secondary data. Information on daily emergency room (ER) visits, from January 1998 to August 1999, as a result of arrhythmia (International Classification of Diseases (ICD-10) 10th revision: I45–I49), only as primary diagnosis, in people older than 17 years of age who live in the city of São Paulo was obtained from the Heart Institute (InCor) of the University

of São Paulo Medical School. Arrhythmias were diagnosed using electrocardiography and classified as one of the following conditions: sinus tachycardia, atrial flutter, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia and ventricular fibrillation. Patients with bradyarrhythmias were excluded. The Heart Institute is the reference centre for cardiovascular disease care and research, receiving cases from all districts of São Paulo city. A permanent staff including at least three medical residents and two assistant professors of cardiology on duty 24 hours a day assures reliable diagnoses. During the study period, 70% of São Paulo's inhabitants were provided with care by the public health system, and 13% of the hospital admissions as a result of cardiovascular diseases among this group were initially attended by the emergency room service of the Heart Institute.[38] In São Paulo, different estimates of the respiratory effects of air pollution have been done using both data from all public hospitals and data from the University of São Paulo Clinics Hospital. The results are similar, which supports the use of data from one medical unit in studies like this one.[39]

Air pollution and weather

Daily records of carbon monoxide (CO), particulate matter with an aerodynamic profile $\leqslant 10$ μm (PM_{10}), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3) were obtained from São Paulo State Sanitary Agency (CETESB).[40] Fourteen monitoring stations were spread around the city, although not all of them measured all pollutants. The measurement adopted for CO (ppm) was the highest 8 hours moving average at eight stations. NO_2 (μg/m^3) concentrations were computed as the highest hourly average at seven stations. The 24-hour averages were adopted for PM_{10} (μg/m^3), measured in 14 stations, as well as SO_2 (μg/m^3), measured in six stations. O_3 was measured in four stations and the highest hourly average was adopted. These computations follow standards adopted by CETESB in agreement with international standards. All pollutants were measured from 1 am to 12 pm. Air pollutant measurements have been analysed around the city in the last 20 years, and air pollution levels recorded in each station are highly correlated with the others. Therefore, the average of all stations that measured each pollutant was adopted as a citywide exposure status. Information on daily minimum temperature and mean relative humidity were obtained from the Institute of Astronomy and Geophysics of the University of São Paulo.

Statistical analysis

We estimated Pearson correlation coefficients between the variables used in the study. Counts of daily total arrhythmia ER visits were modelled for the entire period in generalised linear Poisson regressions.[41] Natural cubic spline[42] was adopted to control for the non-linear dependence of the ER visits in season. The number of knots (or degrees of freedom) of the smoother was chosen to minimise both the autocorrelation of residuals and Akaike's information criteria.[43] When necessary, autoregressive terms[44] were incorporated into the models because autocorrelation plots showed that their serial correlations remained at the residual level.

Extreme temperatures are not usual in São Paulo. However, studies have reported different patterns of effects for temperature on cardiovascular diseases in different cities with distinct temperature patterns.[45] Hence, we explored different sets of temperatures and humidity controls and adopted, in the final models, the maximum temperature of the day (lag 0) and the 3-day average of minimum temperature (lags 1, 2 and 3), simultaneously, to control for potential acute effects of high temperature at lag 0 and the lagged effect of low temperatures. Also, we included lag 0–1 for humidity and indicators for day of the week, to control for short-term trends.

To reduce sensitivity to outliers in the dependent variable, robust regression (M-estimation) was used. Results were expressed as percentage increases in ER arrhythmia visits for interquartile range increases in air pollutant concentrations.

Distributed lag model

Air pollution can induce health effects not only on the same day of exposure but also on subsequent days. Hence, the number of admissions on a given day will depend not only on the same-day effect of that day's pollution but also on the lagged effect of the previous day's pollution. In an unrestricted distributed lag model we have:

$$\log(E(Y)) = \alpha + \text{covariates} + \beta 0 Xt + \ldots + \beta q Xt - q + \varepsilon t$$

where Y is the daily count of admissions, E(Y) is the expected value of that count, and $Xt - q$ is the pollutant/weather concentration q days before the admissions. In this analysis, we adopted a constrained lag structure—that is, a polynomial distributed lag model.[46 47] We investigated the lag structure of air pollution effects on arrhythmia ER visits using a fourth-degree polynomial with 7 days, from lag 0 to lag 6, and 14 days, from lag 0 to lag 13, which imposes constraints, but gives enough flexibility to estimate a biologically plausible lag structure, and controlling multi-colinearity better than an

Table 1 Descriptive analysis of the variables used in this study

Variables	Daily mean	SD	Minimum–maximum	Days of observation
Disease				
Arrhythmia	5.35	2.65	0–16	608
Pollutants				
PM_{10} (μg/m^3)	48.64	20.34	18.68–137.76	608
SO_2 (μg/m^3)	15.05	8.23	2.90–71.47	608
CO (ppm)	3.05	1.37	0.79–10.25	608
NO_2 (μg/m^3)	99.03	39.81	32.0–303.0	608
O_3 (μg/m^3)	68.66	42.64	10.18–389.45	608
Weather				
Minimum temperature (°C)	15.4	3.57	5.20–23.20	608
Maximum temperature (°C)	25.2	4.70	10.20–35.40	608
Relative humidity (%)	81.49	7.8	55.24–96.63	608

Table 2 Spearman correlation coefficients between the main variables used in the study

	Temp*	Hum†	PM_{10}	SO_2	CO	NO_2	O_3
Arrhythmia	−0.096*	−0.077	0.184**	0.284**	0.211**	0.238**	−0.003
Temperature		0.013	−0.258**	−0.414**	0.000	−0.031	0.116**
Humidity			−0.478**	−0.350**	−0.316**	−0.357**	−0.0351**
PM_{10}				0.675**	0.580**	0.781**	0.438**
SO_2					0.360**	0.615**	0.272**
CO						0.641**	−0.009
NO_2							0.479**

*Temp: minimum temperature; †Hum: mean relative humidity; *p<0.05; **p<0.01.

unconstrained lag model. The standard errors of the estimates for each day were adjusted for overdispersion.

After defining the lag structure for each pollutant, we adopted models including lag 0 or moving averages to estimate the cumulative effects of air pollutants in the adopted outcome. If more than one pollutant had a statistically significant effect, we adopted two-pollutant models and total-pollutant models. Also, to explore the presence of thresholds in air pollutant effects, we used categories of air pollutant concentrations (quintiles) instead of continuous variables.

Air pollutant effects are presented as percentage increase (95% confidence intervals, CI) and relative risks for threshold analysis. S-Plus software (version 4.536) was used to carry out the analyses.

This study was approved by the InCor Scientific Board, which provided the authors with secondary data on ER visits.

RESULTS

During the study period, there were 3251 ER arrhythmia visits. Patients' average age was 59.8 (SD 16.1) years; 53.4% were women and 46.6% were men. Table 1 presents the descriptive analyses of the variables.

An arrhythmia ER visit is not a usual event; however, in only 5 days of the study were no arrhythmia ER visits made. Primary pollutants did not surpass their national air quality standards (PM_{10}: 50 μg/m³, annual arithmetic mean, and 150 μg/m³, 24-hour maximum; SO_2: 80 μg/m³, annual arithmetic mean, and 365 μg/m³, 24-hour maximum; NO_2: 100 μg/m³, annual arithmetic mean, and 320 μg/m³, 1-hour maximum; and CO: 9 ppm, 8-hour moving average). Ozone concentration surpassed its 1-hour maximum value (160 μg/m³) in 12 days. It is possible to confirm that São Paulo is not a cold city and most of the maximum daily temperatures observed in the city were between 20°C and 30°C. Humidity was always above 55%.

Table 2 presents Spearman correlation coefficients between dependent and independent variables.

Spearman correlation coefficients between primary pollutants were positive and statistically significant. Correlations between O_3 and other pollutants were positive but smaller and its correlation with CO was negative and non-statistically significant. Arrhythmia presented positive and statistically significant correlations with all primary pollutants.

Figure 1 presents the lag structures of air pollutant effects on arrhythmia ER visits caused by interquartile range increases in air pollutants using fourth-degree polynomials ranging from lag 0 to lag 6. For all primary pollutants, effects were predominately acute and restricted to the same day of the ER visit. For CO, a harvesting effect was clearly observed at lag 1 and the same pattern was observed for NO_2 and PM_{10}. Ozone lag structure was flattened around zero. SO_2 had a different behaviour with a positive effect at all lags but without statistical significance. The same patterns of lag structure were observed when fourth-degree polynomials ranging from lag 0 to lag 13 were adopted.

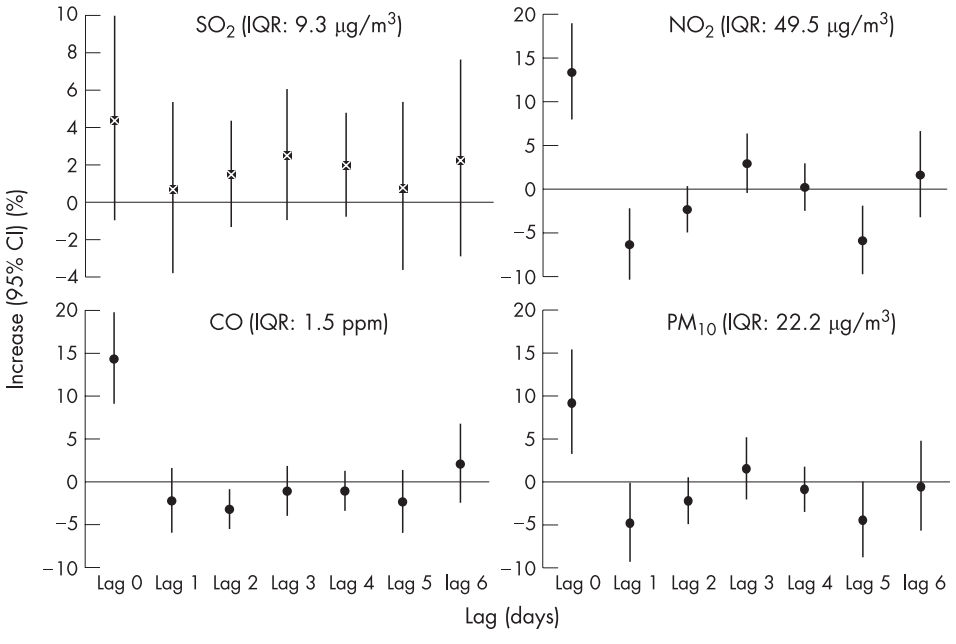

Figure 1 Lag structure of air pollutant effects and 95% confidence intervals on arrhythmia emergency room visits for interquartile range (IQR) increases in SO_2 (9.3 μg/m³), NO_2 (49.5 μg/m³), CO (1.5 ppm) and PM_{10} (22.2 μg/m³) concentrations assessed by fourth-degree polynomial distributed lag models (lag 0 to lag 6).

Table 3 Percentage increases and 95% confidence intervals for arrhythmia emergency room visits caused by interquartile range increases in daily concentrations of PM_{10}, NO_2 and CO, when estimated using three-pollutant and two-pollutant regression models

Pollutant (daily mean at concurrent day)	Interquartile range	Percentage increase	95% CI
Three-pollutant model			
PM_{10} ($\mu g/m^3$)	22.2	−5.6	−12.7 to 2.1
NO_2 ($\mu g/m^3$)	49.5	7.7	−0.3 to 16.4
CO (ppm)	1.5	11.1	5.3 to 17.2
Two-pollutant models			
PM_{10}	22.2	−1.1	−7.0 to 5.1
CO	1.5	12.8	7.2 to 18.7
PM_{10}	22.2	−2.4	−9.4 to 5.1
NO_2	49.5	12.0	4.7 to 19.9
NO_2	49.5	4.0	−1.8 to 10.3
CO	1.5	10.0	4.4 to 15.9

Based on the lag structure results, we developed three-pollutant and two-pollutant models including those that had statistically significant effects in single-pollutant models (table 3).

Only the CO effect remained consistent through the models with different sets of pollutants.

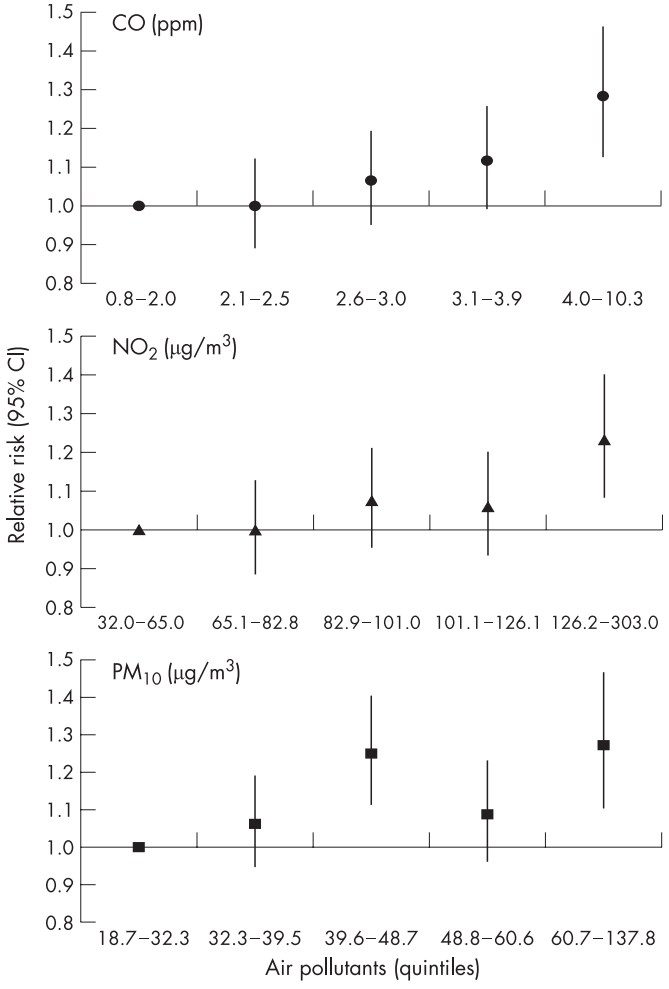

Figure 2 Relative risks and 95% confidence intervals for arrhythmia emergency room visits according to the division of air pollutant daily concentrations in quintiles.

Figure 2 presents estimates of relative risks and 95% confidence intervals for arrhythmia ER visits according to quintiles of CO, NO_2 and PM_{10}. Generally, we found thresholds for gaseous pollutants, with effects starting at the third quintile. For PM_{10}, despite no smooth linear trend, effects had apparently already started at the second quintile and tend to be dose-dependent.

DISCUSSION

In this study, we found a positive association between daily CO, NO_2 and PM_{10} changes and arrhythmia ER visits. The statistically significant effects were acute and limited to the same day of exposure. Also, we observed trends of thresholds for gaseous pollutant effects but not for PM_{10}.

The methodology adopted here has been the standard for time-series analysis. We performed meticulous sensitivity analyses to define the best adjustment for the models and the more adequate set of confounders and covariates, respecting the biological plausibility and statistical parameters. In a time-series study of air pollution health effects based on daily changes of dependent and independent variables some factors may induce effect modification but not confounding. That is the case of gender, age, drug therapies and other risk factors related to both personal habits or characteristics.

Time-series studies of air pollutant effects on cardiovascular morbidity and specifically arrhythmia ER visits are not usual. It makes it harder to compare results. Using different approaches, and following patients with implanted defibrillators, researchers from Boston[32–34] analysed the associations between changes in daily concentrations of air pollutants and the risk of arrhythmia and in general showed effects between 24–72 hours after the exposure. Also they reported that the risk was directly associated with previous and recent arrhythmia events.[32 33] Peters and colleagues[30] have already reported that previous arrhythmia events may act as effect-modifiers of air pollutant effects but found a more extended lag structure 3–5 days after the exposure.

Although we have found a pattern of lagged effects (lag 3) for most of the pollutants, as observed by other researchers[30 35 36] our results consistently point to an acute effect, similar to the findings of Rich *et al*.[33] Particle size and chemical composition may interfere with the mechanism and magnitude of adverse manifestations. Even in those studies that analysed specific kinds of arrhythmias there is no consensus on the lag structure.

We did not have access to the identification or to an instrument that allows hourly records, such as defibrillator

discharges, and worked with calendar-day ER visits and air pollution concentrations. Despite this potential weakness, we found effects with magnitudes similar to those presented in studies performed with more sophisticated epidemiological designs and statistical approaches.[32 33 35]

Despite differences in study designs and pollutant concentrations and compositions, our study and the others mentioned here do not differ substantially. One dissimilarity that deserves mention is that in São Paulo we have found, systematically, relevant associations between health end points and CO, a fact not reported by other authors,[33 34] except in those patients with previously reported arrhythmia.[30 32] As presented in table 1, levels of CO in São Paulo, despite a remarkable decrease during the past two decades, are still higher than those observed in the United States and Europe. Also, we showed that primary pollutants had high day-to-day correlations with each other. It makes it difficult to identify the independent effects of each of them. Hence, it is more plausible to assume that our results support the idea that air pollution generated by cars can be dangerous, leading to increases in cardiovascular morbidity and mortality.

We found thresholds for gaseous pollutants, but particles had a more dose-response pattern. These results are in agreement with those of other researchers who have reported the same pattern for both cardiovascular morbidity[32 33] and mortality.[37]

The acute effect observed in our study could be associated with the possible direct effects of pollutants,[12] involving neural stimulation, changes in autonomic tone leading to reduced heart rate variability, which is recognised as a risk factor for cardiac arrhythmia.[23 24 48] Another hypothesis suggests that inhaled pollutants which cross the pulmonary epithelium into the circulation directly affect the blood coagulability and cardiovascular system.[12 49] A third hypothesis to explain the acute effect is the pulmonary inflammatory process and oxidative stress,[12] with inflammatory mediator release.

Additional hypotheses can also be found in the results of Pekkanen *et al*,[50] which found increased risk of ST segment depression in submaximal exercise testing, performed in patients with stable coronary artery disease, and Brook *et al*[15] who observed constriction in the brachial artery in individuals who inhaled ultra-fine particles and ozone leading to coronary vessel constriction, ischaemia and arrhythmia.

The lagged effect observed for all primary pollutants except CO may be explained by indirect cardiovascular effects of air pollutants which involve pulmonary oxidative stress and systemic inflammation induced by inhaled pollutants as suggested by Brook *et al*.[12] Moreover, we hypothesise that the observed lagged effects may occur among those people without previous or serious cardiovascular illnesses and, hence, who are less susceptible to air pollution effects. Also, different kinds of arrhythmia may induce clinical manifestations with different severity, influencing the time lag of medical attendance, as observed in other studies.[32–34]

One of the limitations of our study is the use of total arrhythmia visits instead of using ventricular and supraventricular diagnoses. However, both kinds of arrhythmia have been presented as susceptible to the effects of air pollution, increasing cardiovascular mortality.[24 25 27 48] Another one is the lack of more precise information about the exact time of arrhythmia manifestation, as occurs in studies using implanted defibrillators, in which the definition of the lag structure between exposure and adverse effect is more accurate.

In summary, the present study showed positive and statistically significant associations between mainly automotive-generated air pollution and arrhythmia ER visits in a way similar to those observed in developed countries. The effects were acute and limited to the same day of exposure. Also, we observed trends in thresholds for gaseous pollutant effects but not for PM_{10}. Although air pollution levels were below standard levels, pollution still affected cardiovascular morbidity, reinforcing the necessity of lowering air pollution standards. To better understand the pathophysiological mechanisms involved in this process that have not been fully addressed, we suggest that additional studies should focus not only on the most highly susceptible groups but also on those with subclinical manifestations of cardiovascular diseases.

What this paper adds

- This study corroborates the association between air pollution and arrhythmia, an important cause of cardiovascular morbidity-mortality.
- The effect observed was acute at lag 0, and it was observed even with pollutant concentrations under the air quality standards.
- The results suggest thresholds for gaseous pollutants, but not for PM_{10}.
- Even though most of the cars in São Paulo run on a mixture of alcohol (23%) and gasoline (77%), which changes the pattern of air pollutant emissions when compared to other urban centres, it was not sufficient to reduce to impact of CO and NO_2 (markers of automotive emissions) on cardiovascular diseases.

Policy implications

- Air pollution is related to cardiovascular disease, the principal cause of the mortality in Brazil and in the world.
- The association between cardiovascular effects and air pollutants with concentrations under the air quality standards demands additional efforts to reduce even more air pollutant emissions.

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