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Isolated and synergistic effects of PM10 and average temperature on cardiovascular and respiratory mortality

Efeitos isolados e sinérgicos do MP10 e da temperatura média na mortalidade por doenças cardiovasculares e respiratórias

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ABSTRACT

OBJECTIVE: To analyze the effect of air pollution and temperature on mortality due to cardiovascular and respiratory diseases.

METHODS: We evaluated the isolated and synergistic effects of temperature and particulate matter with aerodynamic diameter $< 10\,\mu m$ (PM_{10}) on the mortality of individuals > 40 years old due to cardiovascular disease and that of individuals > 60 years old due to respiratory diseases in Sao Paulo, SP, Southeastern Brazil, between 1998 and 2008. Three methodologies were used to evaluate the isolated association: time-series analysis using Poisson regression model, bidirectional case-crossover analysis matched by period, and case-crossover analysis matched by the confounding factor, i.e., average temperature or pollutant concentration. The graphical representation of the response surface, generated by the interaction term between these factors added to the Poisson regression model, was interpreted to evaluate the synergistic effect of the risk factors.

RESULTS: No differences were observed between the results of the case-crossover and time-series analyses. The percentage change in the relative risk of cardiovascular and respiratory mortality was 0.85% (0.45;1.25) and 1.60% (0.74;2.46), respectively, due to an increase of 10 $\mu g/m^3$ in the PM_{10} concentration. The pattern of correlation of the temperature with cardiovascular mortality was U-shaped and that with respiratory mortality was J-shaped, indicating an increased relative risk at high temperatures. The values for the interaction term indicated a higher relative risk for cardiovascular and respiratory mortalities at low temperatures and high temperatures, respectively, when the pollution levels reached approximately 60 $\mu g/m^3$.

CONCLUSIONS: The positive association standardized in the Poisson regression model for pollutant concentration is not confounded by temperature, and the effect of temperature is not confounded by the pollutant levels in the time-series analysis. The simultaneous exposure to different levels of environmental factors can create synergistic effects that are as disturbing as those caused by extreme concentrations.

DESCRIPTORS: Particulate Matter, adverse effects. Temperature. Cardiovascular Diseases, mortality. Respiratory Tract Diseases, mortality. Air Pollution. Time Series Studies.

RESUMO

OBJETIVO: Analisar o efeito da poluição do ar e da temperatura na mortalidade por doenças cardiovasculares e respiratórias.

MÉTODOS: Foram analisados os efeitos da temperatura e do material particulado com diâmetro aerodinâmico < 10 micrômetros (MP$_{10}$), isolado e sinérgico, na mortalidade de indivíduos > 40 anos por doenças cardiovasculares e na mortalidade de indivíduos > 60 anos por doenças respiratórias em São Paulo, SP, entre 1998 e 2008. Três tipos de metodologias foram aplicadas para avaliar a associação isolada: análise de séries temporais com regressão de Poisson, análise *case-crossover* com pareamento temporal bidirecional e análise *case-crossover* com pareamento pelo fator confundidor, i.e., temperatura média ou poluente. Foi interpretada a representação gráfica da superfície resposta, gerada por termo de interação entre tais fatores adicionado à regressão de Poisson, para avaliar o efeito sinérgico entre os fatores de risco.

RESULTADOS: Não foram observadas diferenças entre os resultados das análises *case-crossover* e de séries temporais. Estimou-se mudança percentual no risco relativo para mortalidade cardiovascular e respiratória de 0,85% (0,45;1,25) e 1,60% (0,74;2,46), respectivamente, devido ao aumento de 10 μg/m^3 na concentração do MP$_{10}$. O padrão de associação da temperatura para mortalidade cardiovascular foi de U-*shape* e para mortalidade respiratória foi de J-*shape*, representando maior risco relativo em temperaturas altas. As figuras do termo de interação indicaram maior risco relativo em baixas temperaturas para mortalidade cardiovascular e em altas temperaturas para mortalidade respiratória em níveis de poluição em torno de 60 μg/m^3.

CONCLUSÕES: A associação positiva parametrizada no modelo de regressão de Poisson para os poluentes não sofre confusão da temperatura, bem como o efeito da temperatura não sofre confusão dos níveis de poluentes na análise de séries temporais. A simultaneidade de exposição a diferentes níveis de fatores ambientais pode gerar condições de efeito combinado, tão preocupantes quanto as de extremas concentrações.

DESCRITORES: Material Particulado, efeitos adversos. Temperatura Ambiente. Doenças Cardiovasculares, mortalidade. Doenças Respiratórias, mortalidade. Poluição do Ar. Estudos de Séries Temporais.

INTRODUCTION

Climate change affects human health through a variety of factors and mechanisms.[13] Air temperature is relevant to public health even in developed countries. Extreme temperature events, such as heat waves and cold spells, are a direct cause of mortality.[5,12,14] A study that analyzed mortality data from Catalonia, Spain, between 1983 and 2006, indicated a 19.0% increase in total daily mortality during three consecutive days of extreme heat.[4] Large metropoles, including Sao Paulo, experience remarkable increases in the population necessitating urgent medical care after experiencing intense and long-lasting periods of extreme air moisture.[9,22] Similarly, tropical storms and changes in the rainfall patterns cause structural damage and changes in the patterns of infectious diseases.[8,11]

Air pollution is also responsible for climate change. However, atmospheric concentrations of particulate matter and gases are also associated with health outcomes,[15,18,24] which may become more frequent and intense in the population due to the effect of adverse weather conditions and air quality.[5,7,12] Furthermore, cardiorespiratory morbidity and mortality are significantly associated with both factors.

The characterization of the role of each risk factor helps elucidate the mechanisms involved and implement mitigation and control strategies. However, exposure to pollution and weather conditions occurs simultaneously. Therefore, in addition to their isolated effects, the interaction between these factors must be evaluated by determining whether they act as effect modifiers. The combination of these risk factors can follow simple or complex patterns that can vary geographically, and their characterization can help clarify issues,

define more realistic risk estimates, and establish new guidelines for public health.

This study aimed to examine the effect of both air pollution and temperature on mortality due to cardiovascular and respiratory diseases.

METHODS

Daily mortality data available in the *Programa de Aprimoramento das Informações de Mortalidade* (PRO-AIM – Program for the Improvement of Data on Mortality) of Sao Paulo were selected for the basic causes defined according to the International Classification of Diseases no. 10 (ICD-10). Data on mortality due to respiratory causes (ICD-10-X) were selected for individuals > 60 years old and that due to cardiovascular causes (ICD-10-IX) were selected for individuals > 40 years old between 1998 and 2008.

A case-crossover approach with different types of case-control matching was used. We aimed to better characterize the isolated effect of each risk factor using controls that were intrinsic to the study design and without parameterization. The variability of the mortality rates in the case-crossover analyses was compared between the days of the same month with some similar characteristic, e.g., same day of the week or days with similar temperature values. Therefore, it was ensured that the variability of the outcome was not because of the influence of this variability, and the inclusion of terms to control this variability in the model was unnecessary, as occurs in traditional time-series analyses.

The traditional time-series analysis was also applied. The comparison of the results of the traditional time-series analysis with those of the case-crossover analysis allowed us to examine whether the parameterizations adjusted in the traditional models for factors such as pollution and temperature were accurate or because of confounding factors in the model. The synergistic effects between pollution and temperature were analyzed using response surface analysis of the terms of interaction between the variables, and these terms were added to the Poisson regression model for the time series.

Meteorological parameters were provided by the meteorological station of the *Instituto de Astronomia, Geofísica e Ciências Atmosféricas da Universidade de São Paulo* (IAG-USP – Institute of Astronomy, Geophysics, and Atmospheric Sciences, University of Sao Paulo). Daily maximum temperature data (°C), average temperature (°C), and minimum relative humidity (%) were obtained for the years evaluated.

Air quality data were provided by the *Companhia de Tecnologia de Saneamento Ambiental* (CETESB – Environmental Sanitation Technology Company). We used daily average values for particulate matter with diameter < 10 μm (PM_{10}) from datasets provided by the

air quality stations located in Diadema, Santana, downtown, Sao Miguel Paulista, and Pinheiros. CETESB has 14 air quality stations that automatically monitor PM_{10} levels in the city of Sao Paulo. However, the number and spatial configuration of this network varied considerably over the period evaluated. One station was used in each region of the city, including one in the downtown area, and these stations provided valid data for most of the period evaluated. However, the Parelheiros station was operational at the time of study but its dataset had many gaps and inconsistent observations. Considering that no other station in the Southern region was available during the entire study period, we used data from the Diadema station, which is the neighboring city close to the capital.

During the 11-year study period, not all the 4,018 days covered in the mortality and meteorological datasets were analyzed because of the unavailability of data on air pollution, resulting in a decrease of 13.8% in the data evaluated. The descriptive analysis of variables was performed to characterize their context. We used two main statistical methods to investigate the specific effect of environmental factors on mortality.

Poisson regression analysis was used in generalized additive models to iteratively determine the best structure, linearity, association between mortality and environmental variables, and to define the best control for seasonality as well as long-term tendencies. The logarithm of the number of deaths was dependent on the risk and on the confounding factors described using linear or spline functions, as described by Curriero et al.[7]

Different time lags and moving averages of the explanatory variables were tested. The selection of the most appropriate model structures, i.e., meteorological parameters, lags, and adjusted functions that should be used, was based on the minimization of the Akaike information criterion (AIC)[1] and maximization of the explained variance of the model.

Seasonality was controlled by the inclusion of a non-parametric spline function to a days-elapsed variable. Other temporal tendencies were controlled by introducing variables for weekdays and holidays in the model.

Relative humidity showed a strong linear association and was reallocated in the model as a linear parametric term. The average temperature of the corresponding day was considered the best metric to assess the correlation between temperature and cardiovascular mortality, whereas the two-day moving average of the average temperature was selected to assess the correlation with respiratory mortality. Natural-cubic-spline smoothing functions with degrees of freedom were designated as structures for temperature variables that were selected after analyzing the non-parametric terms. This allowed a better comparison with the results of other analyses. A linear association between pollutant concentration and mortality was assumed. We used the values of the corresponding days for the PM_{10} concentration after testing discrepancies and moving averages.

We compared the results of the time-series analysis with those of case-crossover analysis stratified by time, temperature, or pollutant concentration, using conditional logistic regression models. The case-day exposure was compared with the control-day exposure (period immediately before and after the case-day) by applying the case-crossover methodology, which is a variation of the case-control approach.[6] Using this approach, it is possible to intrinsically control for several invariable confounding factors in the short-term in addition to the control for seasonality. When the control-days are selected in the same month by the approximate value of one of the explanatory variables, i.e., temperature or pollution concentration, this factor can also be controlled without the need for the inclusion of terms or functions for model parameterizations.[21]

This comparative analysis allowed the validation of the results of the Poisson regression analysis. When the case-crossover analysis is matched by period (weekday and month), it generates estimates without confounding factors related to time, weekday, and seasonality. When the case-crossover analysis is matched by period and temperature, estimates are obtained for the association of pollutant concentration without confounding factors related to temperature, which is similar to the time-pollutant matching. If the associations estimated in the traditional analysis using Poisson regression are similar to those estimated in the case-crossover analysis, the parameterizations adjusted in the traditional model captures the effect of each risk factor without confounding it with the effect of other factors. The effect of temperature or seasonality is not attributed to the pollutant concentration.[21]

Control-days were selected in the same month and weekday of the case-day, even for months with similar temperature, i.e., 1°C above or below the rounded temperature value of the case-day, or even for months with similar pollutant concentration, i.e., 2 μg/m³ above or below the rounded concentration value of the case-day for case-crossover matching. Linear terms for PM$_{10}$, spline function with four degrees of freedom for temperature and control for weekday were included when necessary. In addition, we controlled for relative humidity and used the same variables selected in the previous time-series analysis on all models.

The association between the outcome and pollutant concentration generated a β-coefficient and a response curve for temperature in each analysis (traditional, temporal case-crossover, and time-temperature/pollutant concentration stratified case-crossover). We calculated the percentage change in mortality for every variation of the risk factor using the equation $(exp^{β*Δ} - 1) \times 100\%$. The percentage changes in the relative risk were calculated to estimate both the effect of pollutant concentration on mortality due to the increase of 10 μg/m³ in the PM$_{10}$ concentration and their confidence intervals. We extracted the function adjusted for the models to estimate the dose-response association between mortality and temperature, and graphically represented the percentage change in the relative risk due to the variation of 1°C as a function of the metrics of the selected temperature.

The interaction effect between temperature and pollution concentration was characterized by response surface analysis of the interaction term between these variables. This term was included in the additive models generalized in Poisson regression and controlled for seasonality, weekday, holidays, and relative humidity.

Analyses were performed using R software version 3.0.2. The *gam()* function was used for the traditional analysis and *coxph()* function was used for the conditional logistic regression analysis, and a significance level of ≤ 0.05 was adopted.

RESULTS

The average temperature was selected as the best parameter to represent the effect of temperature on the models and the maximum and minimum values were 27.63°C and 7.13°C, respectively (Table 1).

All study variables were essentially correlated (Table 2). The cardiovascular mortality showed a higher correlation with temperature and pollutant concentration

Table 1. Descriptive analysis of the study variables. Sao Paulo, Southeastern Brazil, 1998-2008.

Variable	Average	SD	Minimum	Median	Maximum	NA
Mortality						
Cardiovascular (deaths/day)	55.9	9.7	25	55	96	0
Respiratory (deaths/day)	15.6	5.1	3	15	39	0
Meteorological data						
Average temperature (°C)	19.4	3.4	7.13	19.67	27.63	0
Relative humidity (%)	61.8	16.0	14	60	99	0
Pollutant concentration						
PM$_{10}$ (μg/m³)	45.1	20.8	8.76	40.67	164.30	553

Source: *Programa de Aprimoramento de Informações de Mortalidade da Prefeitura do Município de São Paulo* (PROAIM); *Companhia de Tecnologia de Saneamento Ambiental* (CETESB); *Instituto de Astronomia e Geofísica da Universidade de São Paulo* (IAG).
SD: standard deviation; NA: not available; PM$_{10}$: particulate matter

Table 2. Pearson correlation between mortality and environmental variables. Sao Paulo, Southeastern Brazil, 1998-2008.

Variable	Cardiovascular mortality	Respiratory mortality	Average temperature	Relative humidity	PM_{10}
Cardiovascular mortality	1				
Respiratory mortality	0.28[a]	1			
Average temperature	-0.34[a]	-0.18[a]	1		
Relative humidity	-0.10[a]	-0.12[a]	-0.35[a]	1	
PM_{10}	0.23[a]	0.11[a]	0.08[a]	-0.54[a]	1

PM_{10}: particulate matter
[a] $p < 0.05$

compared to the respiratory mortality. The average temperature and relative humidity were negatively correlated with mortality, whereas the pollutant concentration was positively correlated with health outcomes. The sign of the Pearson correlation index indicated a positive correlation between mortality and PM_{10} and a negative correlation between mortality and temperature. Pollutant concentration and relative humidity showed the most significant negative correlation, reflecting the mechanical removal of many particles on rainy days, which consequently had higher relative humidity.

The percentage change in the relative risk of mortality due to the increase of 10 μg/m³ in the PM_{10} concentration was positive and significant in all analyses (Figure 1). The case-crossover analysis matching time yielded estimates of 0.85% (0.45;1.25) for cardiovascular mortality, which is consistent with the time-series methodology (0.64%; 0.29;1.00). The

case-crossover matching time and temperature estimates (0.67%; 0.21;1.12) proved to be less accurate.

When estimating the effect of PM_{10} on respiratory mortality, a gradual increase in the result between the methodologies used was observed (Figure 1). The lowest value was estimated using the time-series approach (0.8%; 0.14;1.47). The first case-crossover analysis showed results consistent with the previous analysis (1.0%; 0.24;1.73). However, the estimate of the case-crossover analysis matching temperature, although consistent with other PM_{10} estimates, showed a greater effect (1.6%; 0.74;2.46).

The average temperature of the corresponding day was used in the models for assessing cardiovascular mortality whereas the two-day moving average of the average temperature was used for assessing respiratory mortality. Furthermore, the results of the three statistical approaches were consistent (Figure 2).
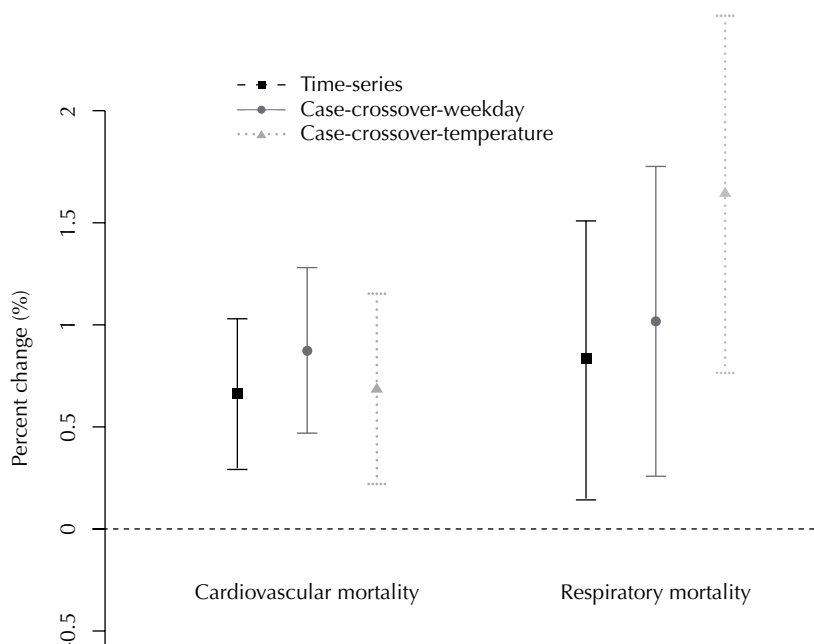

Figure 1. Percentage change in the relative risk for every increase of 10 μg/m³ in the PM_{10} concentration: mortality from cardiovascular disease and respiratory disease. Sao Paulo, Southeastern Brazil, 1998-2008.

A   B

— Time-series
— Case-crossover-weekday
··· Case-crossover-temperature

— Time-series
— Case-crossover-weekday
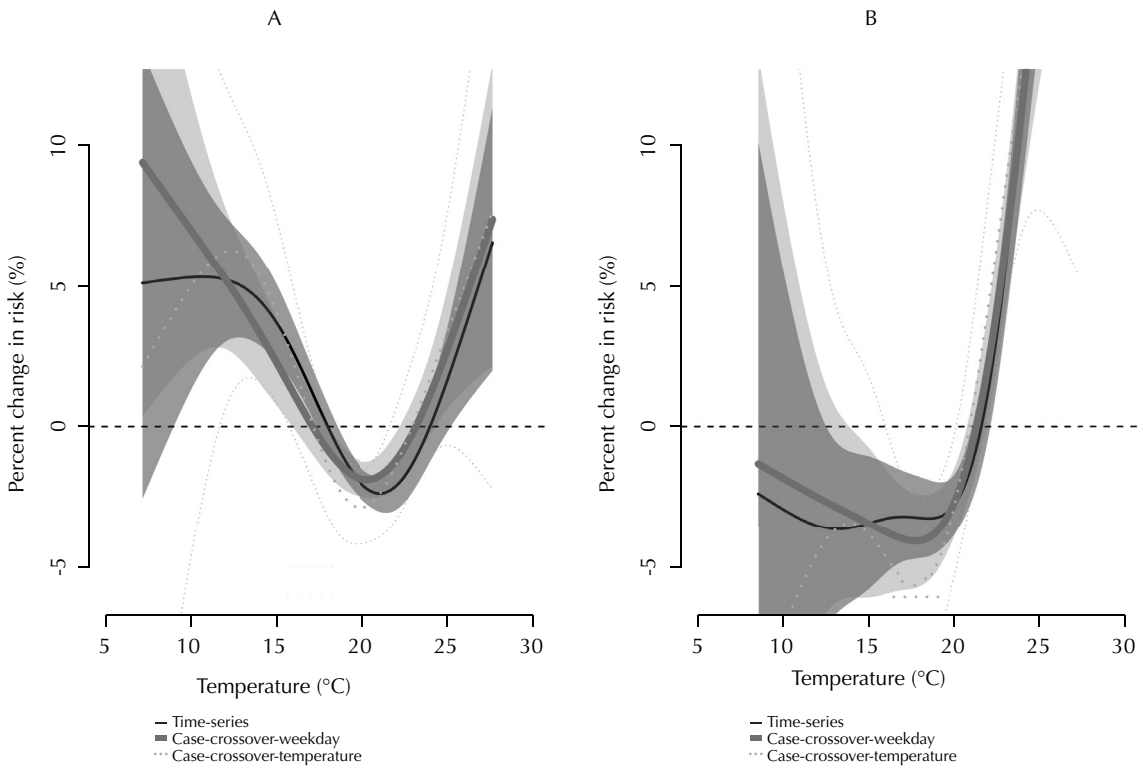··· Case-crossover-temperature

Figure 2. Smoothing functions for average temperatures (cardiovascular mortality): (A) two-day moving average of average temperature (respiratory mortality), (B) confidence intervals; controlled for PM$_{10}$. Sao Paulo, Southeastern Brazil, 1998-2008.

The iterative process defined in each case, the number of degrees of freedom of the dose-response surface for the association between mortality, and the interaction between temperature and particulate matter in the interaction terms are illustratively represented (Figure 3). The linear tendency expected for the association between PM$_{10}$ and mortality was influenced by the effect of temperature, generating surfaces that were more complex.
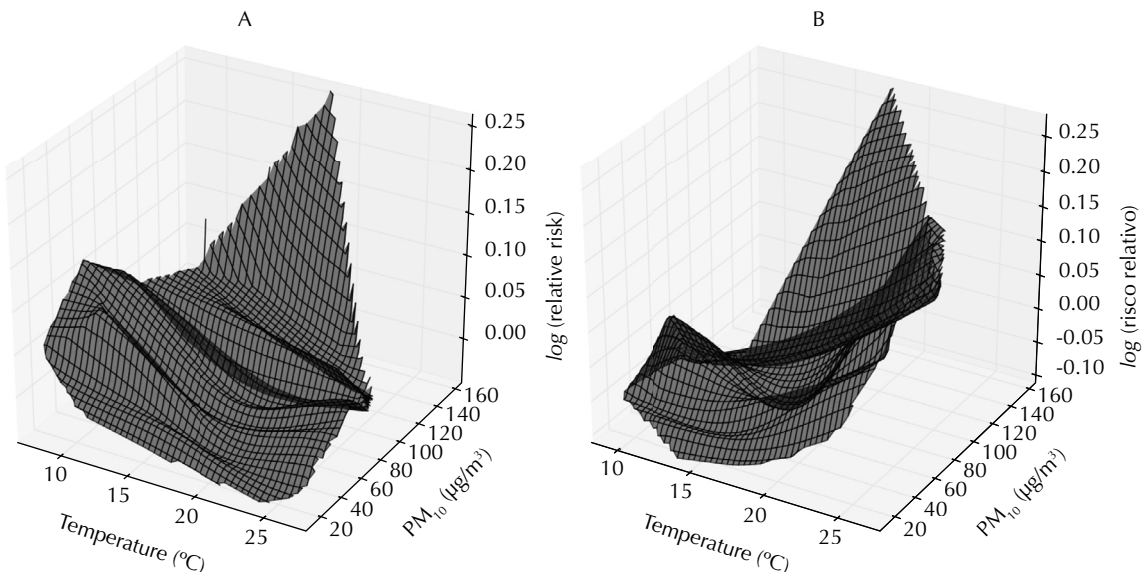
A   B

Figure 3. 3D dose-response surface for the interaction between pollutant concentration (PM$_{10}$) and temperature: (A) cardiovascular mortality, (B) respiratory mortality. Sao Paulo, Southeastern Brazil, 1998-2008.

DISCUSSION

Results of the case-crossover and time-series analyses were similar, indicating that the parameterizations adjusted in the time-series model were effective in determining the impact of temperature and pollutant concentration on mortality. The percentage change in the relative risk of cardiovascular mortality estimated using a case-crossover analysis with temporal matching and the change in the relative risk of respiratory mortality estimated using a case-crossover analysis with temperature matching was about of 0.85% (0.45;1.25) and 1.60% (0.74;2.46), respectively, due to the increase of 10 μg/m³ in the PM_{10} concentration. The pattern of association of temperature with cardiovascular mortality was U-shaped, whereas that with respiratory mortality was J-shaped, indicating increased relative risk at high temperatures. Considering the effect of the interaction between temperature and pollutant concentration, there is a high association under low temperatures on cardiovascular mortality, as well as that under high temperatures on respiratory mortality where the pollutant concentration is approximately 60 μg/m³.

The positive association between PM_{10} and mortality has been previously reported in Sao Paulo and other cities in Latin America and overseas. Saldiva[19] reported this positive association with mortality among individuals > 65 years old in 1995. The multi-city project *Estudio de Salud del Aire y Contaminación en Latinoamérica* (ESCALA)[17] reported a consolidated increase in the relative risk of cardiovascular and respiratory mortalities of 0.7% and 1.2%, respectively, for all age groups. Similar results were found for individuals > 65 years in all of the cities evaluated, including Sao Paulo, between 2006 and 2009.

The association between temperature and mortality has presented more varied patterns in the literature from linear correlations to curves with J, U, and V forms.[2,3,23] Gouveia et al[10] addressed the correlation between all-cause mortality and temperature in the city of Sao Paulo between 1992 and 1994. The U-shaped pattern was identified as the most representative and parameterization was considered linear for the cold weather and linear for the hot weather initiating from an optimum temperature of 20°C. The association with respiratory mortality was higher at lower temperatures but these findings differ from our results. Sharovsky[7] reported similar results for the pattern of correlation between mortality from myocardial infarction and temperature; the temperature of minimum relative risk corresponded to 21.6°C-22.6°C.

The selection of control-days according to the temperature (temperature-time matching) or according to the pollutant concentration (time-concentration matching) yielded values similar to those calculated with two other analyses, the traditional time-series, and case-crossover with temporal matching. Therefore, the positive association between these factors and mortality was not the effect of the confounding factor used in matching.[21] Therefore, the case-crossover methodology is an alternative to the time-series analysis. This avoids the use of parameterization functions for controlling, which must often be user-defined. Similarly, the case-crossover methodology validates the results of Poisson regression models.

We introduced an interaction term between pollutant concentration and temperature in the Poisson regression model to identify the isolated effect of each factor and how the combination of effects occurs. The values generated do not provide easily interpretable estimates for the relative risk but indicate the interactive effect of these factors.

The dose-response surface of the exposure to temperature and particulate matter showed no change in the effect on respiratory mortality. The relative risk of cardiovascular mortality was lower for median concentrations (approximately 40 μg/m³) when combined with median temperatures. The risk at high temperatures was higher than that found at low temperatures in this concentration range. Ren[16] used a similar model in Australia to determine the synergistic effects of PM_{10} and temperature and identified decreases for certain concentration ranges.

The scenario of exposure to environmental risk factors is complex. Other confounders and effect modifiers that are proven to affect associations, including socioeconomic status, demographic developments in long-term studies, and use of air conditioning,[7,20] were not considered in this analysis. Individual-based studies that address the same types of questions can complement the understanding of this dynamics, among many other factors, so that policymakers can plan mitigation actions that are more effective and multisectoral based on consolidated data.

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