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# A spatio-temporal analysis of cause-specific mortality in São Paulo State, Brazil

## Uma análise espaço-temporal da mortalidade por causas específicas no estado de São Paulo, Brasil

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**Abstract** *Using five cause-specific mortality data sourced by the Brazilian Ministry of Health, and over 17 years period, we applied Bayesian spatio-temporal models on 644 municipalities of the state of São Paulo, using logistic model to the binary outcome that specifies whether or not the death was from a specific cause. We modeled the temporal mortality effects using B-splines, while the spatial components were considered through Gaussian and Markov random field, and inference was based on Markov chain Monte Carlo simulation. The results demonstrate consistent downward trend in mortality from infectious and parasitic diseases and external causes, while those from neoplasms and respiratory are rising. Cardiovascular is the only cause-specific death that is kept constant in time. All the causes of death considered show heterogeneous spatial and temporal variations among the municipalities, which sometimes change considerably within successive years. Mortality from infectious diseases clustered around the Northwestern municipalities in 2000, but changes to the Southeastern part in 2016, a similar development as external death causes. The study identifies areas with increased and decreased odds mortality and could be useful in disease monitoring, especially if we consider small spatial units.*
**Key words** *Cause of death, Small areas, Spatio-temporal analysis, Brazil*

**Resumo** *Usando dados do Ministério da Saúde do Brasil para cinco causa de mortes, e num período de 17 anos, aplicamos modelos espaço-temporais Bayesianos em 644 municípios do estado de São Paulo, utilizando um modelo logístico binário que especifica se o óbito foi (ou não) de uma determinada causa. Modelamos os efeitos temporais da mortalidade com B-splines, e os componentes espaciais foram estimados através de campos aleatórios de Gaussiano e Markov. Simulamos a inferência estatística com Monte Carlo via cadeias de Markov. Os resultados demonstraram tendência consistente de queda nas mortes por doenças infecciosas e causas externas, enquanto mortes por neoplasias e doenças respiratórias aumentaram no tempo. Cardiovascular foi a única causa de morte constante no tempo. As causas de morte apresentaram variações espaciais e temporais entre os municípios, com consideráveis mudanças em anos sucessivos. A mortalidade por doenças infecciosas se concentrou nos municípios do noroeste do estado em 2000, mas mudou para a parte sudeste em 2016, um desenvolvimento semelhante as causas externas de morte. Este estudo identificou áreas com maior e menor chances de morte entre diferentes causas, e pode ser útil no monitoramento de doenças, especialmente se considerarmos pequenas unidades espaciais.*
**Palavras-chave** *Causa de morte, Pequenas áreas, Análise espaço-temporal, Brasil*

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## Introduction

Patterns of morbidity and mortality among societies are usually reflections of health care systems, personal lifestyle behavior and the general living conditions of the people, which often vary from one locality to another. The contributions of environmental and geographical settings to the survival chances of people are often enormous[1]. The effects of these factors are accumulated over time and they impact disproportionately on the well-being of people of neighboring locations. These effects, in turn, lead to spatial heterogeneity in risks of morbidity and mortality. Consequently, health geographic studies are important components in understanding disease risk factors and how these risks interact with the natural and built environment.

Over the years, Brazil has undergone structural and economic changes leading to health care reforms that birthed the Brazilian Universal Health System (SUS). With the Law No. 8,080 (also called Organic Health Law), from 1990, the SUS was institutionalized and it became responsible to provide the conditions for the promotion, protection and health recovering for all Brazilian citizens that could not pay a private health insurance. In addition, a second Law No. 8,142, from the same year, established that the community may participate in SUS management, and it also regulated the intergovernmental transfers of financial resources in the social area[2].

Among others, the restructuring altered social structures and affected the pattern of disease and morbidity. Notably, there was a reduction in the burden of infectious and parasitic diseases, but with increase in chronic and non-transmissible diseases[3]. However, records of diseases such as Zika virus, dengue and cholera, and the escalation of malaria and leishmaniasis indicate a non-directional nature of process, though the resurgence of such diseases are said not to have a large impact on mortality trend but a great impact on morbidity[4-6]. So, the epidemiologic transition in Brazil has not followed the known model of the developed world[3].

All these notwithstanding, like other Latin American countries, the Brazilian population has a very heterogeneous health profile that ensures differences in health pattern among different geographical areas and among different social classes[7,8]. Also, the industrial revolution and urbanization experienced in major cities of the country, such as the state of São Paulo, came with additional health challenges related to occupational hazards, accidental intoxication, and injury[9,10]. Frequent family breakdown and illegal drug trade that expose active young people to violence, gangsterism and juvenile criminality in places with high concentration of young adults, has also added to the burden of health issue[11].

Spatio-temporal mapping of public health issues is an important method that allows for the identification of changes in disease patterns over time and, thus, able to unearth the shift in pattern of risk over time and across space. The identification of populations at risk of certain diseases can be useful in management action and serve as tools for planning, monitoring, and surveillance in public health. For instance, progress in previous health interventions at different geographical locations can be ascertained and their effectiveness determined. Further, spatio-temporal approach to analysis of diseases has unique advantage of detecting clusters with high incidence and effectively determines the scope of prevention, when compared with the traditional methods of epidemiology analysis[12,13]. Consequently, researchers have considered the space-time dynamics of various diseases in Brazil such as AIDS[14], dengue[15], visceral leishmaniasis[16], and malaria[17] among others.

In this study, however, we analyze the spatio-temporal dynamics of cause-specific mortality according to disease classification based on the World Health Organization's 10$^{th}$ International Classification of Disease (ICD-10). The analysis was based on data from all municipalities of the state of São Paulo, the most populous and industrialized state in Brazil. This region forms an interesting case, because São Paulo is the most populated state of the country, with almost 46 million inhabitants or 22% of the country's population[18]. Second, some studies have shown that recent death counts registration among municipalities of the state is considered somehow good[19]. This is important as it avoids corrections based on statistical models which often rely on some strong assumptions. The São Paulo state has a considerable number of spatial units, making it possible to analyze heterogeneous spatial distribution of cause-specific mortality.

As addressed by other studies[20], we examined the changes in death profiles, from five ICD-10 chapters, that mainly affect the country namely: infectious and parasitic diseases, cardiovascular diseases, neoplasms, respiratory infections, and external causes, using yearly data from 2000 to 2016. Our aim was to determine if there are spatial clusters of patterns in mortality from each

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of these causes of death overtime and to ascertain if the clusters are consistent over the years in specific municipalities. We also aim to determine the municipalities with high and low risks of death from each cause under study over time. The study equally offers the opportunity to determine if some municipalities in São Paulo suffer from more than one mortality cause over time. Such findings could be also important to aid location-specific health interventions and to reduce the burden of deaths from these causes.

### The configuration of mortality in São Paulo

The state of São Paulo, one of the most developed in Brazil, showed a similar behavior to Brazil in terms of historical gains in life expectancy. The gains were accelerated until the 1960s and modest thereafter[21]. The municipality of São Paulo or state capital, for example, is known for the high quality of information about vital events and for being one of the most developed cities in Brazil[19].

With regard to the reduction of mortality levels, São Paulo municipality was also ahead of the country throughout the demographic transition process[22,23] mostly affected first by reductions in early ages mortality, and a number of socioeconomics developments are from great importance to explain historical infant and child mortality declines. Studies indicate that variables, such as the women's levels of education, availability of piped water and sewage collection for the larger part of the population, and the adoption of basic hygiene and nutrition measures, influenced the general mortality reductions[24,25]. These developments have also played an important role in the mortality and epidemiological transitions that occurred in São Paulo. Considering the mortality profile of the state of São Paulo, since the 1950s, deaths below age five have reduced progressively, due to a great decline in late infant deaths, and this was reflected in infectious and parasitic diseases reductions[26].

At the same time, the share of infectious diseases also lost strength over time, as the proportion of deaths by this cause-specific declined enormously between 1901 and 2000[27]. Other diseases and mortality causes, however, have gained significance in present days, characterized by an increase in deaths from chronic diseases and external causes[27]. For instances, other intra-urban study in São Paulo have shown that mortality rates from external causes of populations living in the worst socio-environmental conditions was more than double, as compared with those living in the developed part of the city. The study also indicates excessive deaths from cerebrovascular diseases, hypertension and traffic accidents among residents aged 45 to 64 years living in areas with worst socio-environmental conditions[28].

## Method

### Data source and level of analysis

Data for this study were obtained from the mortality data made available through the *Sistema de Informações sobre Mortalidade* (SIM), DATASUS, compiled by the Brazilian Ministry of Health (www.datasus.gov.br). The classification of cause-specific mortality was based on ICD-10. We used mortality data collected from all parts of the state of São Paulo from 2000 to 2016, adopting a binary classification that assigns 1 if the death was from a specific cause and 0 if otherwise occurred. The geographical unit analyzed was all the municipalities of the state, which are the smallest administrative unit for which mortality data are registered in Brazil. The period chosen is also important due to geographical disaggregation prior to the baseline year 2000. Hence, spatial comparison is made possible. In all, during this period considered, there were 645 municipalities in the state, but we used 644 localities, excluding one island due to the fact that our spatial approach requires the locations to share geographical boundary with at least another location.

### Statistical method

Spatio-temporal disease mapping techniques have wide application in disease surveillance studies when the interest is to analyze spatial clustering and temporal trend of a disease. Spatio-temporal models extend the standard disease mapping models to allow for the simultaneous analysis of space and temporal components of a given disease. Suppose in our case study, $y_{ijt}$ is a binary outcome that denotes whether or not an individual $i$ living in municipality $j$ at time $t$ died from a cause, say, infectious and parasitic diseases, taking the value 1 if yes, and 0 otherwise. In this case, $y_{ijt} \sim Binomial\ (n_{ijt}, \pi_{ijt})$, where $\pi_{ijt}$ is the proportion of deaths occurring in location $j$ and time $t$. Under the binomial outcome, a *logit*, *probit* or complementary log function can be used to link the predictor $n_{ijt}$ to covariates, which can be in the form of time and space. For easy of result interpretation, we settled for the logistic link function. Excluding subscripts:

$\pi = h(\eta) = exp(\eta) / 1 + exp(\eta)$

and

$\eta = \beta_0 + T + ST$

Where, $\eta$ is the model predictor, $\beta_0$ is the model constant term, $T$ is the temporal term and $ST$ is the spatio-temporal component. To estimate the parameters of the model, we rely on Bayesian approach and assigned prior distributions to the temporal and spatio-temporal components. The temporal part was modeled through Bayesian B-splines (Basis splines) with a second order random walk prior, while for the space-time component, we consider a Markov random field prior and hyperparameters for the prior distributions were based on inverse gamma distribution with parameters a=0.001 and b=0.001. We performed sensitivity analysis by varying the values assigned to the hyperparameters, but the changes do not have much the effects on the estimates. Posterior estimation was through Markov chain Monte Carlo (MCMC) sampling technique implemented through the stand-alone software BayesX, freely available at http://www.bayesx.org/. For each cause of death, we ran 15,000 iterations, setting the burn-in at 2,000 and thinning every 20th observation for parameter estimation to minimize autocorrelation. Convergence was monitored through the trace plot and autocorrelation function of the samples generated. For each cause of death, we fit two models with the first containing only the temporal component (M1), and the second model includes both the spatial and temporal components (M2). The performances of the models were determined through the commonly used deviance information criterion (DIC) and the estimates are presented in Table 1. For all the cause of death, the full spatio-temporal model provided the best fit (smallest DIC) and result presentations shall be based on those of this model.

One limitation of space-time analysis of mortality is usually associated with biases due to the lack of ability to incorporate migration of people, and so, the location of where deaths were recorded may not necessarily link to the environment where it occurred. However, we may assume that the recent migration process in the country is characterized by many municipalities that are stagnated in terms of migration flows, especially in the state of São Paulo[29,30].

## Results

Figure 1 shows the histogram of log mortality (natural log of the number of deaths) based on the 644 municipalities, and reveals the cumulative distribution of the causes of death in the state of São Paulo over a 17 years period. Clearly, none of the cause of death presents evidence of uniform distribution of mortality experience across the municipalities thus, asserting the existence of spatial heterogeneity.

Figure 2 presents the posterior mean estimate for the temporal patterns of the causes of death considered. Each plot from the Figure was derived from the results of the Bayesian B-splines prior included in the spatio-temporal model. As it evidences, mortality due to infectious diseases and external causes reduced drastically over the years, though a slight rise is seen in the case of external causes between year 2000 and 2001, and 2010 and 2011. On the other hand, mortality from neoplasms and respiratory infections are on the rise, increasing sharply from low levels in year 2000, when deaths from external and infectious diseases were peaked, to higher levels in year 2016. Deaths from cardiovascular diseases, however, follow a pattern that is different from the other four causes. It presents a trend that reduces between year 2000 and 2002 and then rises slightly up to 2004, followed by another slight reduction in 2005 from where it rises to peak in the year 2009, before another pattern of reduction

**Table 1.** Values of the deviance information criterion (DIC) for two models estimated. Five causes of death, municipalities of São Paulo from 2000 to 2016.

| Model | Infectious diseases | Cardiovascular diseases | Neoplasms | Respiratory diseases | External causes |
|---|---|---|---|---|---|
| M1 (Temporal only) | 1245766.208 | 4446767.231 | 3268133.201 | 2153913.981 | 2152346.063 |
| M2 (Spatio-temporal) | 1241480.731 | 4430422.819 | 3256063.474 | 2150438.534 | 2140958.429 |

Source: Brazilian Ministry of Health, 2000 to 2016.

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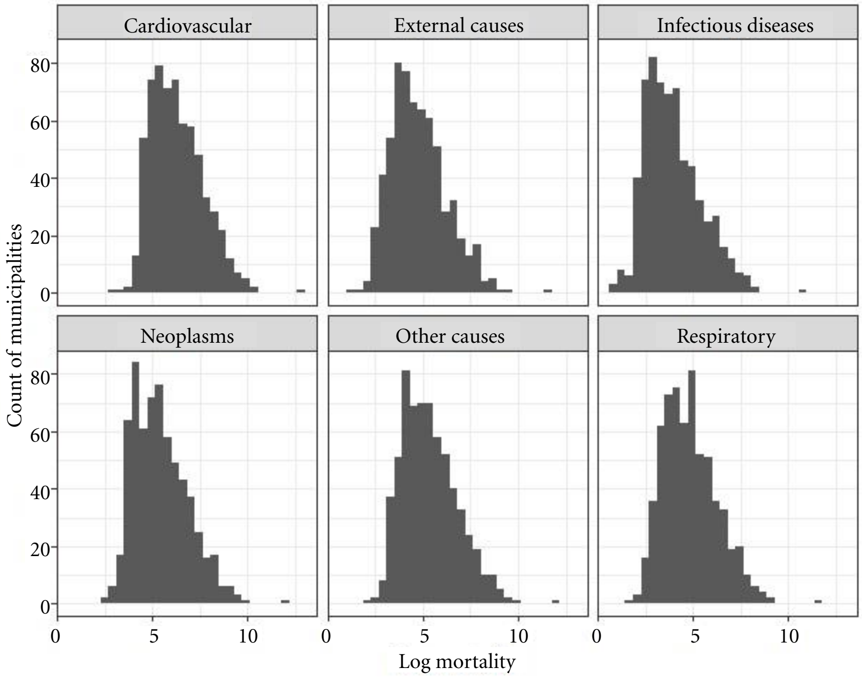


**Figure 1**. Histogram of logarithm of count cause specific mortality for all the 644 municipalities of state of São Paulo 2000-2016.

Source: Brazilian Ministry of Health, 2000 to 2016.

that spans till the year 2013. After this, there are, however, new signs of rising mortality for this group of deaths.

We present, in Table 2, the percentage distribution of the total deaths for each cause of death based on the age and sex for years 2000, 2008, and 2016. In addition, we tested differences in proportions, considering the year 2000 as baseline for comparison. The purpose is to see how the distribution of deaths was associated with important demographic indicators, such age and sex population distributions, over the selected period. As revealed by this Table 2, mortality from infectious diseases among children aged 0-5 years was 8.8% in year 2000, and this has steadily reduced, by half of its value (4.42%) in 2008 and to 2.61% in 2016. However, among the elderly population, the proportion of mortality from infectious diseases went in opposite direction, increasing from 24.05% to 45.83% between 2000 and 2016. Over the 17 years period, the variation in the proportion of mortality of cardiovascular diseases among the 65 plusses was minimal, increasing from 63.1% in 2000 to 67.9% in 2016, and the same can be said to other age groups. This may explain the almost constant trend of this death cause verified in Figure 2.

If we consider neoplasms deaths, there is a similar temporal development to those of cardiovascular diseases, we verify small percentage reductions among the young children, and certain increasing from 53.38% to 57.65% among the elderly. On the hand, the respiratory deaths followed a similar path as infection illnesses, with strong reduction of its proportions among children and expressive increase of its numbers when we consider elderly population. In the case of mortality from external causes, as expected, the proportion of mortality was highest among individuals aged 21-40 years old throughout the period, but these percentage estimates have reduced over the 17 years. Regarding sexes differences, male generally recorded the highest proportion than female for all death causes, with notably huge differences in the case of death from external causes.

In the case of results of the spatio-temporal patterns, to allow for proper comparison, we present in Figure 3, the thematic maps drawn for the years 2000, 2008 and 2016, which are the

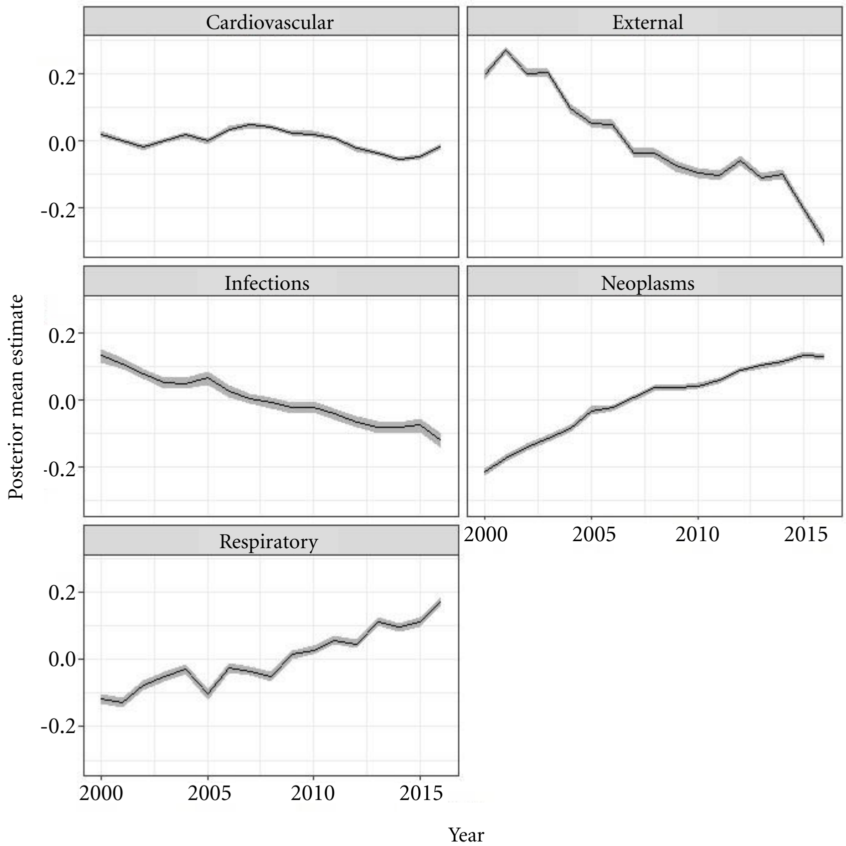


**Figure 2.** Posterior mean estimate for temporal effects of cause-specific mortality in the state of São Paulo, 2000-2016.

Source: Brazilian Ministry of Health, 2000 to 2016.

base, mid and last year of understudy, respectively. These maps have been drawn using the free software R-4.0.2 for Windows.

The odds ratio mortality from the analysis were plotted such that the risks of mortality from a particular cause of death is considered high if the odds ratio is greater than unity for a municipality and low if it is less than unity. As revealed in the Figure 3, deaths from all the analyzed causes form interesting spatial clusters, some of which change rapidly over the years. For instance, in the year 2000, deaths from cardiovascular diseases show a high-high concentration of deaths around the Southwestern and Northwestern parts of the state, and this spatial pattern persists during the years 2008 and 2016, with some forms of spread towards a few hotspots in the North of São Paulo in the last year of the study. Yet, deaths from external causes present a consistent high concentration of clusters with high-high mortality in municipalities around the extreme Southeastern parts of the state and this pattern remains and spread in this region of São Paulo throughout the study periods.

In the case of mortality from infectious and parasitic diseases, considering the baseline year, 2000, there were high-high clusters of mortality for this death cause located in Northwestern parts of São Paulo. In 2008, however, the clusters though persisting in those areas, they were not as highly concentrated, when compared to the year 2000. By the year 2016, there was a complete reversal as compared to the first year of analyses, in which mortality from this cause become concentrated in the Southeastern and few hotspots in Northern parts of São Paulo.

Mortality from neoplasms are concentrated more around municipalities in the Northwest-

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**Table 2.** Percentage of deaths by cause disaggregated by age and sex for years 2000, 2008 and 2016 in São Paulo.

| Cause of death | Infectious diseases (%) | p | Cardiovascular diseases (%) | p | Neoplasms (%) | p | Respiratory (%) | p | External Causes (%) | p | Others Causes (%) | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Year 2000[#] (Base line year)** | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| 0-5 | 8.8 | | 0.91 | | 0.79 | | 5.6 | | 2.61 | | 23.3 | |
| 6-20 | 1.93 | | 0.51 | | 1.63 | | 1.13 | | 20.81 | | 5.47 | |
| 21-40 | 32.22 | | 4.91 | | 5.98 | | 5.45 | | 49.06 | | 18.52 | |
| 41-65 | 32.99 | | 30.56 | | 38.23 | | 20.03 | | 20.36 | | 24.76 | |
| >65 | 24.05 | | 63.1 | | 53.38 | | 67.79 | | 7.17 | | 27.95 | |
| Sex | | | | | | | | | | | | |
| Male | 63.56 | | 52.77 | | 55.01 | | 56.02 | | 85.65 | | 64.64 | |
| Female | 36.44 | | 47.23 | | 44.99 | | 43.98 | | 14.35 | | 35.36 | |
| Total deaths | 10,976.00 | | 99,085.00 | | 36,391.00 | | 24,862.00 | | 23,416.00 | | 41,171.00 | |
| **Year 2008** | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| 0-5 | 4.42 | *** | 0.57 | *** | 0.56 | *** | 2.22 | *** | 1.95 | *** | 16.54 | *** |
| 21-40 | 20.6 | *** | 4.19 | *** | 4.87 | *** | 3.7 | *** | 42.18 | *** | 10.25 | *** |
| 41-65 | 40.61 | *** | 28.95 | *** | 38.36 | ns | 19.21 | * | 27.45 | *** | 26.71 | *** |
| >65 | 32.3 | *** | 65.79 | *** | 55.03 | *** | 74.15 | *** | 15.19 | *** | 43.84 | *** |
| Sex | | | | | | | | | | | | |
| Male | 60.32 | *** | 52.69 | ns | 54.52 | ns | 53.7 | *** | 81.23 | *** | 57.62 | *** |
| Female | 39.68 | *** | 47.31 | ns | 45.48 | ns | 46.3 | *** | 18.77 | *** | 42.38 | *** |
| Total deaths | 9,897.00 | | 104,437.00 | | 45,204.00 | | 28,900.00 | | 19,501.00 | | 40,133.00 | |
| **Year 2016** | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| 0-5 | 2.61 | *** | 0.39 | *** | 0.34 | *** | 1.23 | *** | 1.84 | *** | 11.44 | *** |
| 6-20 | 1.39 | ** | 0.55 | *** | 0.82 | *** | 0.61 | *** | 9.94 | *** | 2 | *** |
| 21-40 | 12.91 | *** | 3.94 | *** | 4.48 | *** | 3.25 | *** | 34.7 | *** | 6.95 | *** |
| 41-65 | 37.27 | *** | 27.22 | *** | 36.71 | *** | 19.49 | *** | 28.39 | *** | 23.44 | *** |
| >65 | 45.83 | *** | 67.9 | *** | 57.65 | *** | 75.43 | *** | 25.13 | *** | 56.17 | *** |
| Sex | | | | | | | | | | | | |
| Male | 56.5 | *** | 52.53 | ns | 53.17 | *** | 52 | *** | 76.93 | *** | 53.42 | *** |
| Female | 43.5 | *** | 47.47 | ns | 46.83 | *** | 48 | *** | 23.07 | *** | 46.58 | *** |
| Total deaths | 10,669.00 | | 117,399.00 | | 55,158.00 | | 41,422.00 | | 18,241.00 | | 52,299.00 | |

[#]Differences in proportion are tested based on Z-test and considering year 2000 as benchmark. ***p<0.001, **p<0.01, *p<0.05 and "ns" is not significant.

Source: Brazilian Ministry of Health, 2000 to 2016.

ern parts of the state in the years 2000 and 2008, and then moving its concentration to the East and South of the state in 2016. In addition, as for respiratory infections, mortality followed a similar spatial and temporal pattern, as compared to cancer related diseases. This was concentrated towards the Northern and Western municipalities, presenting similar patterns in the years of 2000 and 2008, but there was a shift towards the Southern and Eastern parts, during the last year of analyses.

A cross comparison of the spatial clusters formed by the five causes of death reveal that during the year 2000, while residents of the Western and Northern municipalities had higher concentration of deaths from infectious and parasitic diseases, those from the Southeastern parts suffered more from external causes of death. However, by the year 2016, it was evident that there was a concentration of deaths from infectious diseases, external causes, neoplasms and respiratory infections in the Southeastern

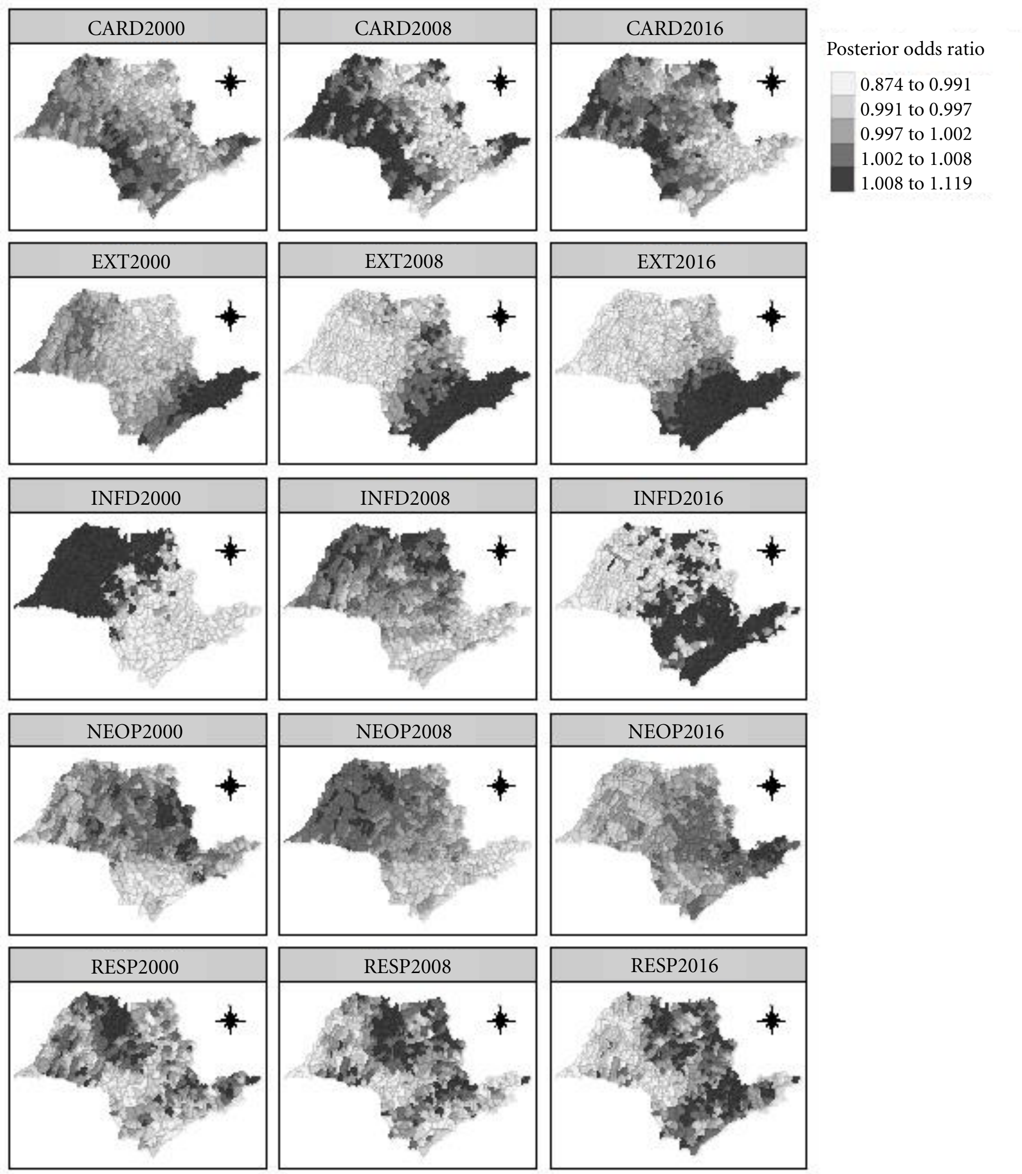


**Figure 3**. Thematic maps of the state of São Paulo showing the spatiotemporal estimates for cause-specific mortality during years 2000, 2008, and 2016.

Note: CARD: Cardiovascular diseases; EXT: External causes; INFD: Infectious and parasitic diseases; NEOP: Neoplasms causes; RESP: Respiratory infections.

Source: Brazilian Ministry of Health, 2000 to 2016.

municipalities of São Paulo, while cardiovascular deaths were kept concentrated in the Western municipalities of the state.

## Discussion of results

In this study, we examined the space-time patterns of mortality due to five causes of deaths in the municipalities of São Paulo, using a Bayesian modeling method that allows us to examine the

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relationships across time and space. This descriptive analysis revealed that the cumulative distributions of each of the five causes of deaths have not been uniformly distributed overtime and in space, but proving the existence of variations across the municipalities with many localities recording similar experiences, forming spatial clustering.

Our findings indicate, among municipalities, a consistent downward trend in mortality from infectious and parasitic diseases and external causes, while those from neoplasms and respiratory are rising. Cardiovascular is the only cause-specific death that is kept almost constant during the period considered. The spatial analyses also show clusters and hotspots that are geographically distinguished by cause-specific deaths.

Additionally, our results show that external causes and deaths related to infectious diseases follow similar temporal and spatial patterns between the 17 years of study. In accordance with these findings, epidemiological literature also shows consistent decline in mortality from infectious and parasitic diseases and external causes in the country and in the state of São Paulo. There are documented evidence that support that morbidity and mortality from infectious and parasitic diseases have reduced consistently since the 1950s throughout Brazil, which are reflections of the consistent interventions in healthcare and living conditions of the population[26].

According to Mendes[31], since 2000, there has been a significant reduction in homicide deaths in the state of São Paulo, which represented a different evolution from that observed in the rest of the country. This support the evidence of decline of these two causes of deaths, which are the results of years of local government interventions, and various reforms and policies destined to reduce deaths from both causes, even though these causes of death are still considered "unfinished agenda" in Brazil[3,32].

Among others, reduction in deaths from motor accidents in the state of São Paulo has been noted in the last 20 years due to a policy that saw to the reduction of average speed of motor vehicles with the decline more recorded among individuals aged 50 years or older[33]. Improvement in social conditions, increased access to education, and policing also helped in preventing homicide and violent crimes in the state[34,35]. Following these developments, the spatial and time analyses pointed out that deaths related to the infectious illnesses has shifted its spatial pattern through time, going from West to Southeast of São Paulo. This can be explained partially by the changes in terms of economic production that has occurred in the Western parts of the state. The West of São Paulo was historically characterized by municipalities involved in agricultural economic activities[36,37], which in turn are highly correlated with infectious diseases[38]. At the turn of XXI century, these areas moved away from the traditional agriculture in exchange for modern agro-industry, and the production of commodities to exportation[39]. Hence, in the last period, these causes of death became concentrated in the most industrialized and urbanized municipalities in Southeastern of the state[40]. The same analyses are valid for external causes of death, which are highly positive correlated with degrees of urbanization[41], because urbanized municipalities usually present increasing risks of deaths due to traffic accidents and homicides[42].

Notwithstanding, several studies have pointed out the positive and rising relationships between air pollution and respiratory and cardiovascular problems in the city of São Paulo, particularly among the elderly and children[43]. This is also seen through our results, especially concerning deaths associated with respiratory illnesses, which are concentrated in the Southeastern and Northern municipalities of the state, in more industrialized and urbanized regions[40]. Cardiovascular related deaths, however, are more spread and its spatial pattern has not changed much across the state and over time.

We may believe that, for cardiovascular causes of death, other underlying factors could influence its spatial distribution. In Brazil, two reasons attributed to the rise in cardiovascular deaths in particular are lifestyle changes that have to do with urbanization and globalization characterized by higher caloric intake and lower energy expenditure, and populations aging resulting from gains in life expectancy and lower fertility rates[32].

On the other hand, our findings also indicate the persistence rise in mortality from neoplasms causes in the municipalities of São Paulo, as one evidence of the constant increase in noncommunicable diseases as the communicable ones decline. In São Paulo, some studies have shown, even among young adults, a slight rise in all cancer types and a marked rise in brain cancer particularly among males[44]. Among the municipalities, to a lesser extent, we equally observed a spatial evolution in the direction of Southeastern parts of the state, the same areas of clusters as observed for the other diseases.

For the causes of death considered, the study identified spatial patterns for each specific mortality risks, which have shifted considerably through time. The findings have also shown that all the causes of deaths present heterogeneous spatial and temporal variations among the municipalities of the state of São Paulo, which sometimes change considerably within successive years. At the same time, some causes of death especially cardiovascular related deaths, show similar temporal as well as spatial developments.

It should be noted that the causes of death considered here are lump up of several specific-causes and a further disaggregation would have been necessary to disentangle the contribution of each cause across space and time. However, this was beyond the scope of this study as our intention was to provide the spatio-temporal picture of the main causes of death across the municipalities of São Paulo. It is our believe that the findings from this study offer useful tools for disease monitoring, especially as it considers very small spatial units, and improvements in health profiles of the municipalities at different scales could affect changes in the pattern of death among them and in turn, in Brazil.

## Collaborations

All the authors drafted the manuscript and critically review its intellectual content.

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