



# Trends in morbidity and mortality from COPD in Brazil, 2000 to 2016

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## ABSTRACT

**Objective:** To examine the trends in overall COPD mortality, as well as trends in in-hospital morbidity and mortality due to COPD, in Brazil, and to validate predictive models. **Methods:** This was a population-based study with a time-series analysis of cause-specific morbidity and mortality data for individuals  $\geq 40$  years of age, obtained from national health information systems for the 2000-2016 period. Morbidity and mortality rates, stratified by gender and age group, were calculated for the same period. We used regression analyses to examine the temporal trends and double exponential smoothing in our analysis of the predictive models for 2017. **Results:** Over the study period, COPD mortality rates trended downward in Brazil. For both genders, there was a downward trend in the southern, southeastern, and central-western regions. In-hospital morbidity rates declined in all regions, more so in the south and southeast. There were significant changes in the number of hospitalizations, length of hospital stay, and hospital expenses. The predictive models for 2017 showed error rates below 9% and were therefore validated. **Conclusions:** In Brazil, COPD age-adjusted mortality rates have declined in regions with higher socioeconomic indices, where there has been an even sharper decrease in all in-hospital morbidity and mortality variables. In addition to factors such as better treatment adherence and reduced smoking rates, socioeconomic factors appear to be involved in controlling COPD morbidity and mortality. The predictive models estimated here might also facilitate decision making and the planning of health policies aimed at treating COPD.

**Keywords:** Pulmonary disease, chronic obstructive/mortality; Pulmonary disease, chronic obstructive/epidemiology; Socioeconomic factors.

## INTRODUCTION

The prevalence of COPD has increased worldwide and is now considered the third leading cause of death.<sup>(1,2)</sup> In Brazil, the overall COPD mortality rate showed a trend toward an increase between 1998 and 2004, and a decline from 2004 to 2009. In the 1998-2004 period, that rate increased in all regions of the country, declining thereafter only in the southern and southeastern regions.<sup>(3)</sup> The pattern for the age-adjusted COPD mortality rate was similar to that observed for the overall rate.<sup>(4)</sup>

Morbidity related to the natural history of COPD, especially infectious exacerbations and hospitalizations, is also considered relevant, as are smoking-related diseases, which are responsible for considerable morbidity and mortality, especially in the more severe forms of COPD.<sup>(5-9)</sup> Those factors contribute to increased absenteeism at work and early retirement, thereby promoting an increase in the direct and indirect costs associated with the disease.<sup>(10-12)</sup>

In Brazil, the history of public health policies to control smoking and prevent COPD began approximately three decades ago, culminating in a reduction in the prevalence of smoking in the country.<sup>(13,14)</sup> However, measures

aimed at treating COPD are more recent developments, involving the distribution of inhaled medications provided at no cost by public health facilities, thereby benefiting patients undergoing specialist care. Adherence to treatment is one of the main objectives of the follow-up of patients with COPD. Some authors have shown that the rates of treatment abandonment are higher among women and among individuals who visit a specialist less frequently.<sup>(15)</sup> Other authors have reported that higher treatment adherence rates are associated with optimal socioeconomic conditions.<sup>(16)</sup>

Because Brazil is a country of continental dimensions, comprising macro-regions with different socioeconomic characteristics, a time-series analysis of COPD-related morbidity and mortality would aid in the evaluation of prevention strategies and current treatment. Therefore, the aims of this study were to examine the temporal trends in COPD mortality rates in the various macro-regions and to evaluate the temporal trends in in-hospital morbidity and mortality related to COPD, as well as to estimate and validate predictive models for the rates and variables considered.

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## METHODS

### *Study design and setting*

This was an ecological, population-based, analytical exploratory study with a time-series analysis of data related to the morbidity and mortality associated with COPD in Brazil. The dataset was limited to individuals  $\geq 40$  years of age and to the period of January of 2000 to December of 2016.

Public-use data were obtained from the information systems of the Brazilian National Ministry of Health and the Information Technology Department of the Brazilian Unified Health Care System,<sup>(17)</sup> including death certificates (sorted by place of residence), the number of hospitalizations, and length of hospital stays, all identified as related to COPD as defined in the International Classification of Diseases, 10th revision (ICD-10). Data for the resident population, based on the two most recent demographic censuses (2000 and 2010) and on population estimates for the non-census years (2001-2009 and 2011-2017), by age group, are publicly accessible and were obtained from the Brazilian Institute of Geography and Statistics.<sup>(18)</sup>

### *Study participants*

The study population consisted of individuals  $\geq 40$  years of age residing in Brazil during the study period.

### *Statistical analysis*

In this study, COPD was defined as a condition meeting the criteria of ICD-10 codes J41-J44. The ICD-10 codes J40 and J47 were not included, the first because it did not specify whether the disease was acute or chronic and the second because it referred to bronchiectasis, a term that, in Brazil, is closely associated with the sequelae of pulmonary tuberculosis.

The variables used in the time-series analysis were selected on the basis of a preliminary analysis of the data obtained for the number of deaths, the age-adjusted mortality rate by place of residence, the number of hospitalizations, the length of hospital stays, and hospital expenses.<sup>(19,20)</sup> In addition, these outcomes were stratified by geographic macro-region (north, northeast, central-west, south, and southeast), by gender, and by age group (40-49, 50-59, 60-69, 70-79, and  $\geq 80$  years).

For each macro-region, the annual mortality rate per 100,000 population was calculated on the basis of the number of deaths from COPD/resident population, stratified by gender and age group. To determine the change in mortality rates from 2000 to 2016, the 2016:2000 ratios for each macro-region were then calculated, also by gender and age range.

The annual in-hospital COPD age-adjusted mortality rates were determined by calculating the ratio between the number of deaths and the number of persons by place of residence during the year in question, multiplied by 100,000 and then multiplied by the percentage distribution of the standardized population. The data

regarding the population adopted for standardization was obtained from the 2010 census.<sup>(18-20)</sup>

The annual number of hospitalizations was defined as the total number of hospitalizations due to COPD recorded in a given year. The length of hospital stay referred to the total number of days of hospitalization. Finally, the total hospital expense was defined as the cost of hospitalization during the period. The defined underlying causes of death were then recorded for the period from January of 2000 to December of 2016, and the COPD mortality rates were calculated, by place of residence, for the years 2000 and 2016, after which the 2016:2000 ratio was calculated by gender, age group, and macro-region.

To analyze the temporal trend during the studied period, we identified the regression equation that best described the relationship for each outcome, by gender and macro-region. For the hospital outcomes (age-adjusted in-hospital mortality rate, number of hospitalizations, length of hospital stay, and hospital expenses), we calculated the average annual percentage change (APC) in the indicators for the entire study period and the APC estimated for each time segment detected, with the respective 95% confidence intervals, from the regression model, using the Joinpoint Regression Program, version 4.6.0.0 (National Cancer Institute, Bethesda, MD, USA). In the APC analysis, inflection points were used in order to test whether a segmented line is significantly better than a straight line and whether a line with many segments is better than a line with fewer segments. To find the number of significant joinpoints, we used a permutation test.<sup>(21)</sup>

Finally, we performed an analysis involving double exponential smoothing, with the aim of estimating the age-adjusted in-hospital mortality rate, as well as the number and duration of hospitalizations due to COPD for the year 2017, using Minitab Statistical Software, version 18.0 (Minitab Inc., State College, PA, USA). The models were chosen by optimizing the parameters and measures of accuracy, including the mean absolute percentage error, the mean absolute deviation, and the mean squared deviation. The model selected was the one that minimized those three combined measurements. The final model was validated by calculating the percentage error between the observed and estimated values for the year 2017, with a significance level of 5%.

### *Ethical aspects*

The data used in this study were from a secondary, anonymized source, available for public use and providing no information regarding individual identification. The study was approved by the local research ethics committee (CAAE no. 0055691.18.1.0000.5200; Protocol no. 2.954.260).

## RESULTS

In Brazil, COPD was the fourth leading cause of death from 2000 to 2006, the fifth leading cause

of death from 2007 to 2014, and the fourth leading cause of death again from 2015 to 2016 (Figure 1). We observed variations in the 2016:2000 ratio for the COPD mortality rate among the macro-regions of the country. In the northern, northeastern, and central-west regions, the ratio was greater than 1.00 for both genders and in most age groups (Figures 2A, 2B, and 2C), whereas it was less than 1.00 for both genders and in all age groups in the southern and southeastern regions (Figures 2D and 2E). In the country as a whole, the 2016:2000 ratio for the COPD mortality rate was lower than 1.00 in both genders and in all of the age groups studied, indicating a downward temporal trend (Figure 2F). Figures 2J, 2K, and 2L show that there was an exponential increase in the COPD mortality rate in parallel with advancing age, with a similar presentation in the years 2000 and 2016, regardless of gender or macro-region.

In Brazil as a whole, there was a significant downward trend in the COPD mortality rate for both genders (Table 1). In the southern, southeastern, and central-western regions, there was a downward trend for both genders, whereas there was an upward trend in the other macro-regions. The number of hospitalizations and the length of hospital stays demonstrated a downward trend across Brazil and in all macro-regions, with a sharper reduction in the south and southeast (Table 1).

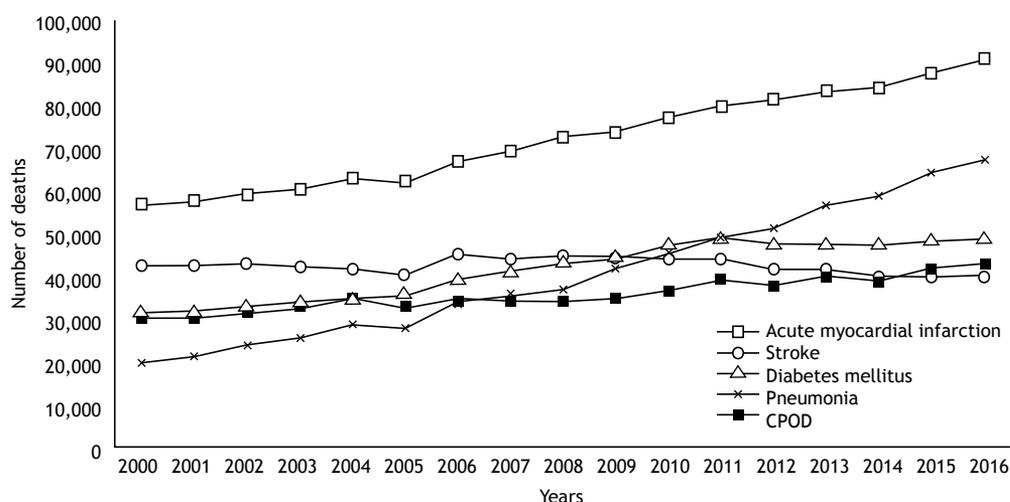
The joinpoint analysis for the in-hospital COPD mortality rate demonstrated a significant negative average APC for both genders (Table 2). The number of hospitalizations due to COPD and the length of hospital stay presented a negative, significant average APC for both genders, with a slight reduction in the APC for females from 2009 onward (Table 2). Hospital expenses presented a negative average APC for both genders, and the difference was significant for males. Until 2003, the APC was negative and significant for both genders, thereafter becoming positive only for females.

The predictive model estimates for in-hospital mortality rates, number of hospitalizations, and length of hospital stay are presented in Figure 3. All of the models presented mean absolute percentage errors of less than 7%. The values observed for the year 2017 were contained in the intervals with a 95% confidence interval and presented a percentage error of less than 9%, thereby validating the predictive models (Table 3).

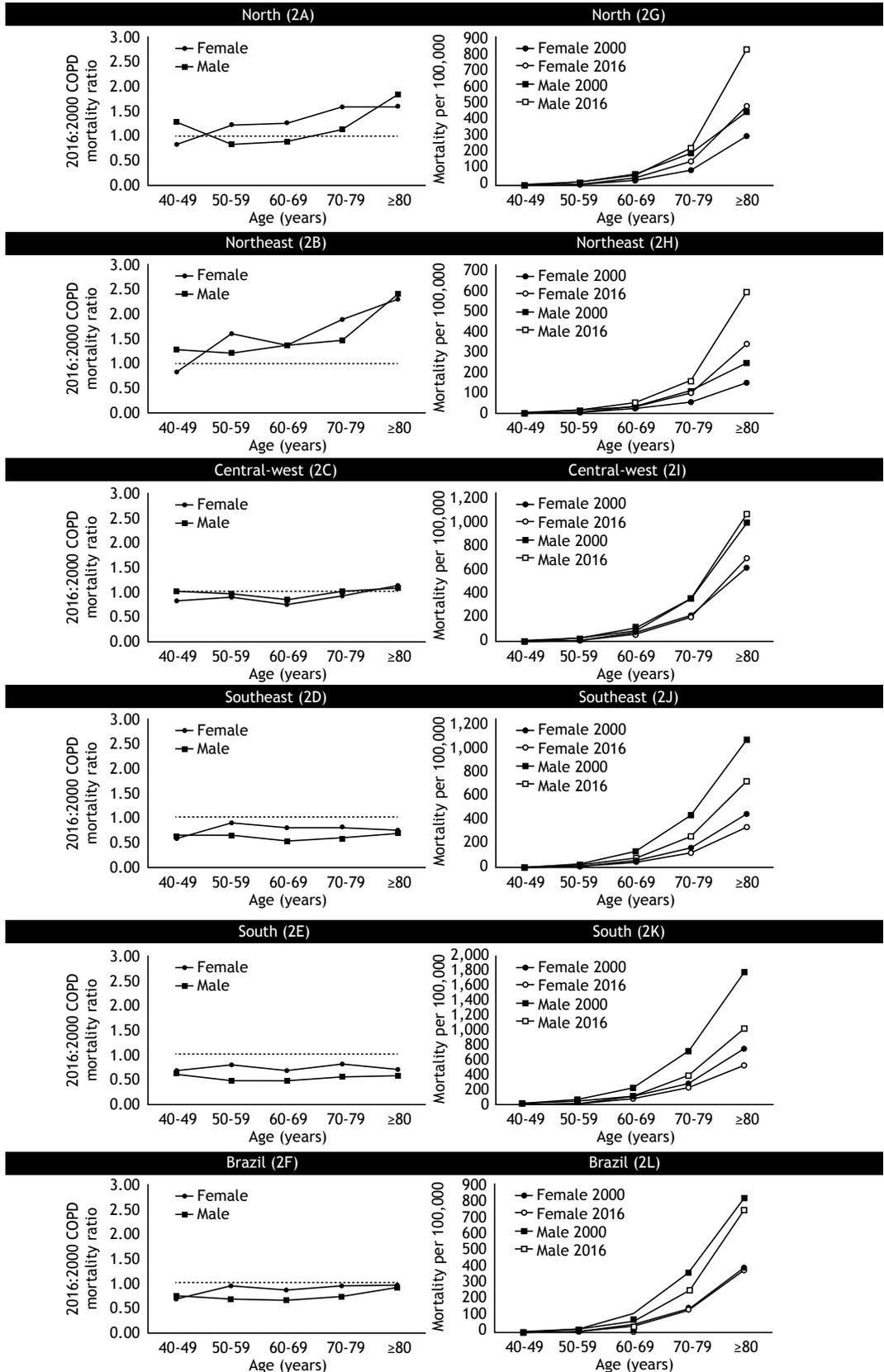
## DISCUSSION

We highlight two main findings of the present study. First, we observed a downward temporal trend in the COPD mortality rates in the macro-regions with higher socioeconomic indices.<sup>(22,23)</sup> Second, we observed a downward temporal trend in the in-hospital morbidity outcomes (number of hospitalizations, length of hospital stay, and hospital expenses) and mortality indicators in all regions, with a far more pronounced decrease in the regions exhibiting more favorable socioeconomic conditions.

In Brazil, the COPD age-adjusted mortality rate presented a significant decrease in both genders. This is similar to one study<sup>(1)</sup> that suggested that the decline in COPD mortality rates observed in certain countries is related to an increase in the gross income per capita in those countries. Within this context, our findings show that the COPD age-adjusted mortality rate presented different patterns in the southern, southeastern, and central-western regions of the country, where there were decreases for both genders, whereas there were increases in other regions. According to Brazilian Institute of Geography and Statistics data, the southern, southeastern and central-western regions have the lowest proportions of people with low incomes, the least social inequality, the lowest illiteracy rates in individuals  $\geq 40$  years of age, and the greatest proportional participation in the gross domestic product, in comparison with the



**Figure 1.** Trends of the underlying causes of death, according to the International Classification of Diseases, 10th revision, in Brazil, 2000-2016.



**Figure 2.** 2016:2000 COPD mortality ratios (A-F) and COPD mortality rates for the years 2000 and 2016 (G-L), by region, gender, and age group in Brazil, 2000-2016.

**Table 1.** Regression analysis for the age-adjusted mortality rate per 100,000 population, number of hospitalizations, and length of hospital stay, by gender and by region, among individuals with COPD in Brazil, 2000-2016.

Variable	Females		Males	
	$\beta$	R <sup>2</sup>	$\beta$	R <sup>2</sup>
<b>Age-adjusted mortality rates</b>				
Brazil	-0.2*	85.8	-0.4*	91.3
North	0.0	0.0	-0.1	16.7
Northeast	0.0	1.3	0.0	2.6
Southeast	-0.2*	86.5	-0.5*	91.4
South	-0.4*	85.3	-1.3*	92.2
Central-west	-0.3*	88.8	-0.4*	79.6
<b>Hospitalizations</b>				
Brazil	-4,057.7*	92.2	-5,352.9*	95.4
North	-122.5*	87.5	-155.4*	91.3
Northeast	-516.5*	81.8	-569.6*	89.9
Southeast	-1,162.8*	87.5	-1,594.5*	93.1
South	-1,839.9*	92.5	-2,505.7*	95.1
Central-west	-416.0*	95.2	-527.8*	94.6
<b>Length of hospital stay, days</b>				
Brazil	-18,603.6*	83.1	-29,801.0*	93.7
North	-545.5*	79.3	-710.7*	81.7
Northeast	-1,032.1	18.7	-2,708.6*	79.9
Southeast	-5,666.9*	74.3	-9,513.5*	92.0
South	-9,932.7*	89.6	-14,640.5*	93.4
Central-west	-1,426.4*	48.9	-2,227.7*	86.0

$\beta$ : beta coefficient; and R<sup>2</sup>: coefficient of determination. \*p < 0.05.

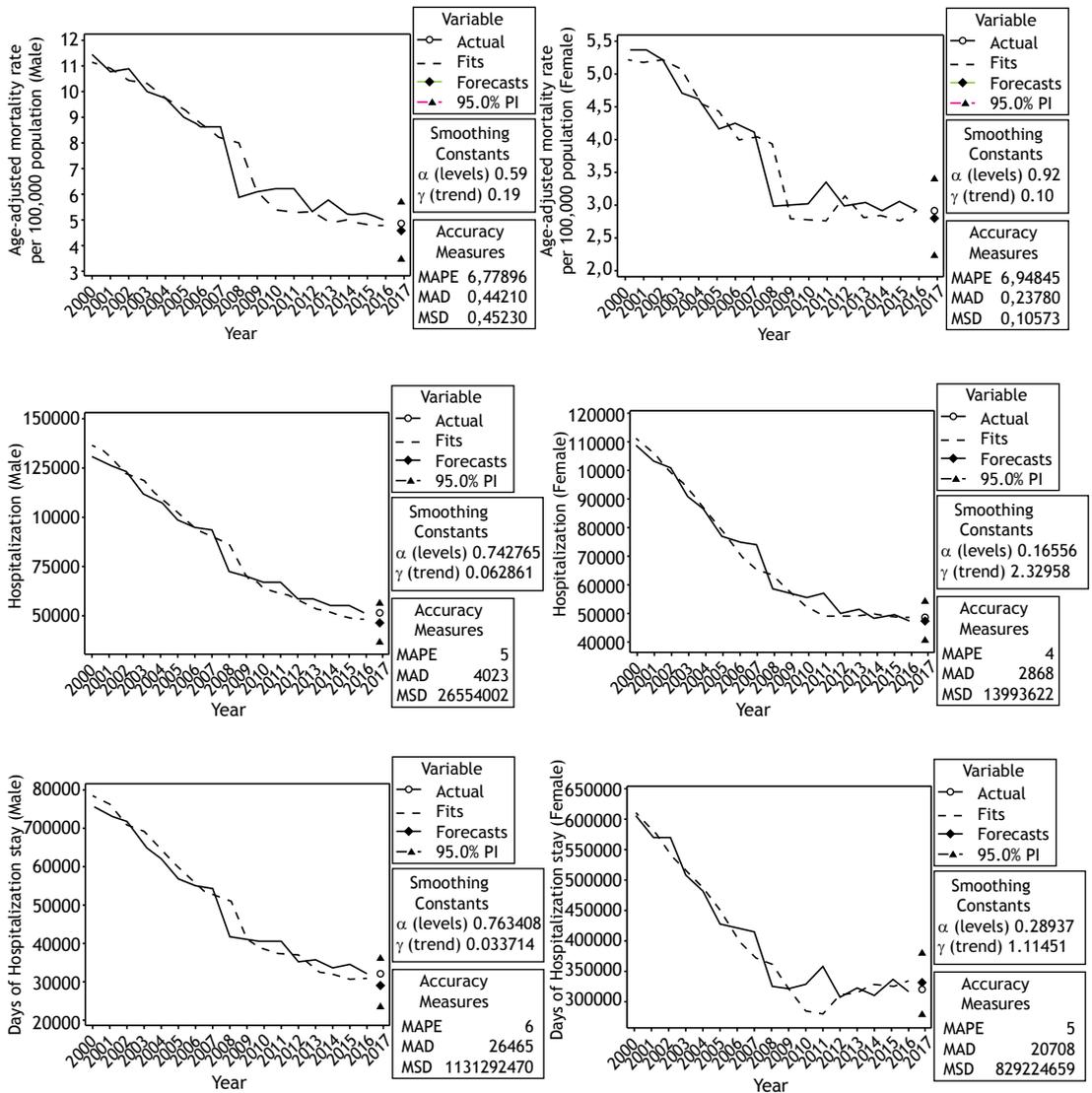
**Table 2.** Joinpoint regression, standardized by age and gender, for in-hospital mortality rate, number of hospitalizations, length of hospital stay, and hospital expenses for COPD in Brazil, 2000-2016.

	Average APC	95% CI	Trend 1		Trend 2		
			Years	APC	95% CI	Years	APC
<b>In-hospital mortality</b>							
Male	-5.6	(-6.3 to -4.8)	2000-2016	-5.6	(-6.3 to -4.8)		
Female	-4.2	(-5.1 to -3.3)	2000-2016	-4.2	(-5.1 to -3.3)		
<b>Hospitalizations</b>							
Male	-6.2	(-6.8 to -5.7)	2000-2016	-6.2	(-6.8 to -5.7)		
Female	-5.4	(-6.3 to -4.5)	2000-2009	-7.1	(-8.3 to -6.0)	2009-2016	-3.2 (-4.9 to -1.4)
<b>Length of hospital stay, days</b>							
Male	-5.7	(-6.3 to -5.0)	2000-2016	-5.7	(-6.3 to -5.0)		
Female	-4.1	(-5.2 to -3.0)	2000-2009	-6.8	(-8.2 to -5.4)	2009-2016	-0.5 (-2.7 to 1.7)
<b>Hospital expenses</b>							
Male	-1.3	(-2.4 to -0.2)	2000-2003	-7.3	(-12.8 to -1.4)	2003-2016	0.1 (-0.5 to 0.8)
Female	-0.6	(-1.9 to 0.7)	2000-2003	-9.8	(-16.1 to -3.1)	2003-2016	1.6 (0.9 to 2.4)

APC: annual percentage change.

other macro-regions.<sup>(23-25)</sup> Although we observed an increase in COPD mortality rates in the north and northeast regions between 2000 and 2016, an annual telephone survey showed a significant reduction in the proportions of smokers in all regions of the country from 2006 to 2014.<sup>(26)</sup>

Corroborating our findings of a decline in COPD age-adjusted mortality rates in the regions with higher socioeconomic indices, a hospital-based study conducted in Denmark reported higher adherence and lower mortality rates among individuals with a higher income, although it should be borne in mind



**Figure 3.** Double exponential smoothing model for age-adjusted in-hospital COPD mortality rates, number of COPD-related hospitalizations, and length of COPD-related hospital stays (in days) for females and males in Brazil, 2000-2016. MAPE: mean absolute percentage error; PI: prediction interval; MAD: mean absolute deviation; and MSD: mean squared deviation.

that Denmark is a country with an equitable health care system and better income distribution than that occurring in Brazil.<sup>(16)</sup> The decline in COPD mortality we observed in southern, southeastern, and central-western Brazil, in both genders and all age groups, also suggests a possible association between socioeconomic indicators and COPD mortality rates.

The decrease in in-hospital morbidity observed in all regions of Brazil might have been influenced by the availability of inhaled COPD medication at no charge from public health facilities. Since 2013, the federal government of Brazil has guaranteed the availability of short-acting and long-acting bronchodilators (adrenergic  $\beta_2$  agonists and anticholinergics), as well as inhaled corticosteroids, a responsibility that was previously borne by the states.<sup>(27)</sup> In fact, several studies have demonstrated that regular use of inhaled

medications reduces the number of exacerbations and hospitalizations due to COPD.<sup>(28-30)</sup> However, the fact that there was decline in in-hospital morbidity and mortality in the south, southeast, and central-west of Brazil supports the hypothesis that socioeconomic indices play a role in in-hospital COPD morbidity and mortality. In addition, if we consider that better socioeconomic conditions also have a positive influence on adherence to treatment in patients with chronic diseases, the findings of Tavares et al.<sup>(31)</sup> also validate our results. Those authors reported that individuals living in the south and southeast of Brazil are more likely to adhere to treatment.<sup>(31)</sup>

We also expected that the negative APCs for the number and duration of hospitalizations would be more pronounced in recent years. It is possible that the uneven distribution of inhaled COPD medication

**Table 3.** Comparison of values estimated by the predictive model for 2017, in relation to the values observed in the same year, for age-adjusted in-hospital mortality rate, number of hospitalizations and length of hospital stay for COPD in Brazil.

Variable	Actual	Forecast	Error (%)*	95% CI
Age-adjusted in-hospital mortality rate				
Male	4.98	4.61	7.43	3.53
Female	2.95	2.80	5.08	2.22
Hospitalizations				
Male	50,156	45,818	8.65	-55,673
Female	47,986	47,528	0.95	-54,554
Length of hospital stay (days)				
Male	327,355	301,384	7.93	-366,221
Female	322,894	330,940	2.49	-381,673

\*((Actual – Forecast)/Actual) × 100.

throughout the country or discontinuity in its distribution during certain periods contributed to a less pronounced negative APC for the number of hospitalizations after 2009. The access to inhaled COPD medication at no charge provides the best control of the disease, which may have resulted in the hospitalization of only the more severe cases due to the natural evolution of the disease, as well as smoking-related comorbidities, consequently requiring longer hospital stays. Other factors, such as nonadherence to treatment, the increase in the life expectancy of the population in the last decade, and the ceiling effect of the drug distribution program—the greatest impact occurring in the first years of such programs—can also be considered to explain these findings.

Finally, the predictive models validated for the year 2017 demonstrated the ongoing downward trend in the in-hospital morbidity and mortality due to COPD in Brazil, although the amplitude of the confidence intervals enables higher estimates than those currently reported. The results of the present study could lay the groundwork for the development and validation of additional predictive models, controlling for socioeconomic indicators, which could increase the accuracy of the estimates.

This study has some limitations. First, we chose to use official data in the public domain, the source of which contains death certificates from the Brazilian National Ministry of Health Mortality Database, therefore being secondary data that are subject to inconsistencies and gaps. That data source does not present information regarding spirometry findings or the severity of COPD. Second, we did not have access to information on the use of inhaled COPD medications. That information is registered in the municipal pharmacies that are responsible for the distribution of such medications and is not in the public domain.

Our findings suggest that factors related to the distinct socioeconomic conditions observed in the various macro-regions of Brazil are involved in the control of COPD-related morbidity and mortality, as are factors already addressed in the literature, such as adherence to treatment and a reduction in smoking rates. It is possible that improving economic conditions will promote reductions in the rates of morbidity and mortality associated with COPD. Our predictive models could assist in decision making and in the planning of health policies for the treatment of COPD.

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