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ORIGINAL PAPER

Excess mortality in a cohort of Brazilian patients with a median follow-up of 11 years after the first psychiatric hospital admission

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Abstract

Purpose To estimate the mortality rates of a cohort of Brazilian patients after their first psychiatric admission and determine the possible risk factors associated with excess mortality.

Methods The study included a cohort of psychiatric patients hospitalised from Jan 1, 2002 to Dec 31, 2007 in the catchment area of Ribeirão Preto, São Paulo state, Brazil. Data were linked to deaths that occurred between Jan 1, 2002 and Dec 31, 2016 from the SEADE Foundation (state data analysis system of São Paulo). The mortality rate (MR), age-sex-standardised mortality ratio (SMR), life expectancy at birth, and years of life lost (YLL) were computed. The factors associated with mortality were analysed by survival analysis using a Cox proportional hazards regression model.

Results Of 4019 patients admitted (54.76% male), 803 died (69.74% male) during the follow-up (median = 11.25 years). Mortality rates were approximately three-fold higher than expected (SMR = 2.90, 95% CI 2.71–3.11). The highest mortality rate was noted in men with alcohol-related disorders (SMR = 5.50, 95% CI 4.87–6.19). Male sex (adjusted hazard ratio (aHR) = 1.62, 95% CI 1.37–1.92), higher age (aHR = 21.47, 95% CI 13.48–34.17), and unemployment (aHR = 1.22, 95% CI 1.05–1.43) significantly increased the mortality risk from all causes. The average YLL was 27.64 years with the highest YLL noted in nonalcohol substance-related disorders (39.22 years). The life expectancy at birth in this cohort was 47.27 years. Unnatural causes of death were associated with nonwhite skin colour and substance-related disorders.

Conclusion An excess of mortality and a significant reduction in life expectancy of mentally disordered patients who were first admitted to psychiatric beds was noted, particularly patients admitted for substance-related disorders, which should represent a priority in mental health policies.

Keywords Mortality · Mental disorders · Low- and middle-income countries · Years of life lost · Causes of death

Introduction

People with mental disorders are more likely to die prematurely than the general population with an estimated relative risk (RR) of 2.22 (95% CI 2.12–2.33) and 10 years of life lost according to a meta-analysis [1] that included studies from 29 countries.

The risk is not similar for all mental health problems, and the underlying causes of death can also vary [2, 3]. Individuals suffering from severe mental disorders, especially psychotic disorders [4], depressive disorders [5], and comorbid substance use disorders [6], are at higher risk of mortality and significantly reduced life expectancy [7], and approximately 20 years of life is lost [8, 9].

In addition, patients who have undergone psychiatric hospitalisation are generally more seriously ill individuals and, therefore, have an increased risk of premature mortality [10], especially deaths from suicide [11]. Several studies that integrate a recent meta-analysis [10] indicate that the risk of mortality is especially high soon after discharge from psychiatric hospitalisation.

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The excess mortality in mental disorders is currently well documented for high-income countries (HICs), mainly in Europe and North America. Of the 203 studies included in the meta-analysis cited above [1], only ten were from low- and middle-income countries (LMICs), of which only one was from Brazil. Information regarding the health consequences of mental disorders in LMICs is relevant given that these countries, predominantly located in Africa, Asia, and Latin America, represent more than 85% of the world's population [12] and are responsible for almost all premature deaths (30 to 69 years) from noncommunicable diseases (NCDs) that occur worldwide [13].

The few studies about the mortality rates in mental disorders conducted in LMICs, contradict the belief that the evolution and prognosis of psychoses would be more benign in LMICs than in HICs [14]. Evidence suggests that the association between mental disorders and mortality in LMICs may be similar to or even higher than those estimated for HICs. For instance, studies performed in Ethiopia have reported a standardised mortality ratio (SMR) between 2.14 (95% CI 1.77–2.56) [15] and 5.98 (95% CI 4.09–7.87) [16]. In Asia, the SMR varied from 1.62 (95% CI 1.57–1.68) [17] in Korea to 6.80 (95% CI 6.30–7.40) [18] in Central Asia. The only study in Latin America with Brazilian patients admitted to a psychiatric hospital showed mortality rates (SMR = 8.40, 95% CI 4.00–15.90) [19] greater than those registered in other LMICS.

Many changes have occurred in the Brazilian mental health policies since the 1990s, with the definitive implementation of the Unified Health System (SUS) and the reform of the psychiatric system when Brazil started to follow international guidelines for treatment and offer free medical care to all Brazilians. However, the lack of current data reduces the visibility of premature mortality in mental disorders and hampers the defence of its inclusion as a priority in health care initiatives.

Given the relevance of updated estimates for countries with significant social inequalities and severe economic constraints, we aimed to estimate the mortality rates in individuals from a cohort of Brazilian patients after their first psychiatric admission and to determine possible risk factors associated with excess mortality and the causes of premature death. We hypothesised that our patients would have higher mortality rates and lose more years of life than patients from HICs.

Methods

Context of the study

This study was conducted in the Ribeirão Preto catchment area, located in the state of São Paulo, Brazil. The state of São Paulo comprises 645 municipalities and is the most developed state in Brazil, accounting for 31% of the country's gross domestic product (GDP). Life expectancy at birth of individuals in the state of São Paulo (75.04 years) was approximately 2 years greater than the average for Brazil (73.48 years) according to the last Brazilian Census of 2010 (https://cidades.ibge.gov.br/). The Ribeirão Preto catchment area comprises 26 municipalities in a territorial area of 10,852 km^2 with 1,328,535 inhabitants and a population density of 122.42 inhabitants/km^2. The Human Development Index (HDI) for this region ranged from 0.69 to 0.80. Ribeirão Preto is the main municipality of the region with 604,682 inhabitants. The median population of the remaining 25 municipalities was 23,871 (range from 1953 to 110,094), and the region's economy is mainly based on agribusiness.

The public mental health services network in the Ribeirão Preto catchment area is a regionalized system. Each community-based service is responsible for a specific catchment area regardless of the patient's diagnosis or severity of the mental disorder. The inpatient units are closely connected with each other and with community-based services. When this cohort was started, the Ribeirão Preto catchment area had 108 psychiatric beds: 6 in an emergency hospital, 22 beds in psychiatric wards in a general hospital, and 80 beds in a psychiatric hospital.

Study design

This is a longitudinal study based on medical records of a cohort of psychiatric patients (described in [20]) admitted between 2002 and 2007 to the public network of mental health services in the Ribeirão Preto catchment area. The cohort data were linked to the SEADE Foundation database (state data analysis system of São Paulo—https://www.seade.gov.br/), and the date and causes of death were collected. The SEADE Foundation uses deterministic linkage methods between patient records and death records (Supplementary Fig. S1). The outcome was deaths that occurred in the state of São Paulo from Jan 1, 2002 to Dec 31, 2016. This study followed the RECORD guidelines for reporting observational studies (Supplementary Table S1).

Inclusion and exclusion criteria

We included all patients admitted for the first time to psychiatric beds distributed in three inpatient units (psychiatric hospital: 80 beds; general hospital: 22 beds; emergency unit: 6 beds) of the Ribeirão Preto catchment area from Jan 1, 2002 to Dec 31, 2007. First-admitted patients were identified in administrative databases provided by each inpatient unit, which were combined into a single database. We included

patients who remained hospitalised for more than 12 h independent of the diagnoses.

Patients whose information regarding date of birth or mother's name was missing in the original database were excluded, as it prevented the identification of the individuals in the SEADE Foundation database where information on date and causes of death could be collected.

Data collection

The beginning of the follow-up was considered the date of the first psychiatric admission, and the end of the follow-up was the date of death informed in the death certificate or Dec 31, 2016. The information available in the database obtained at the first hospital admission includes (a) sociodemographic data, including sex, age, occupation (employed/homemaker/student; unemployed), marital status (single/divorced/widowed; married/partnered), and city of origin (Ribeirão Preto; other municipalities); (b) psychiatric diagnosis according to Section V of the 10th edition of the International Classification of Diseases (ICD-10), including alcohol-related disorders (F10), nonalcohol psychoactive substance use disorders (F11–F19), psychotic disorders (F20–F29), mood disorders (F30–F39) and other mental disorders (F00–F09, F40–F48, F50–F59, F60–F69, F70–F79, F80–F89, and F90–F98 and F99); and (c) characteristics of hospital admission, including length of stay (in days), year of admission (2002–2007) and inpatient unit (psychiatric hospital, emergency unit, and general hospital). Regarding occupation and marital status, data were missing in 75 (1.86%) and 97 (2.41%) patients, respectively. To optimise our sample size, we imputed missing data using the Multiple Imputation by Chained Equations (MICE). The information available in the database obtained on the death certificate includes (a) sociodemographic data, including sex, age, skin colour (white; black/mixed/yellow) and marital status (single/divorced/widowed; married/partnered); and (b) information regarding death, including date, municipality of death (Ribeirão Preto; other municipalities), and cause of death according to the ICD-10, including natural causes (A00-R99) and unnatural causes (V01-Y98).

Statistical analysis

We first performed a descriptive statistical analysis of the sample and follow-up data. We then estimated mortality rates (MRs) per 1000 person-years with 95% confidence intervals (95% CIs) for each exposure category. We estimated standardised mortality ratios (SMRs) with 95% CIs, adjusted for age group (10–14, 15–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80 +) and sex. We used the indirect method of standardisation, and we used data from the population of Ribeirão Preto from the last demographic census of 2010 (mid-follow-up period) as a standard population. In this reference population, the number of deaths for that period was 3,915 in 604,682 inhabitants (data obtained from the Brazilian Census Bureau—https://www.ibge.gov.br/). We calculated the life expectancy according to Chiang's method of abridged life tables with age intervals of 5 years [21]. Life expectancy was calculated for the entire cohort based on sex and diagnosis categories. The years of life lost (YLL) were calculated based on the difference between the age in death and expected age of death according to the annual actuarial life table from the SEADE Foundation for the period 2002–2016 divided by the number of deceased persons. The YLL reflects the years of life that the patient would have lived if the corresponding life expectancy had been fulfilled. We calculated average YLLs with 95% CI for each sex and diagnosis category. Survival analyses were then conducted to identify characteristics associated with overall mortality using Cox proportional hazards regression models (univariate and multivariate). We calculated hazard ratios (HRs) with 95% CIs for the univariate and multivariate models. Model 1 was adjusted for all covariates, and Model 2 was adjusted only for significant covariates in Model 1 ($p < 0.05$). The proportional hazard assumption was analysed with Cox's proportional hazards test based on Schoenfeld residuals and visual inspection of log–log plots. The association of sociodemographic characteristics registered in the death certificate with mortality from natural and unnatural causes was also calculated. A survival analysis from the first hospital admission to death or the end of the observation was also computed using Kaplan–Meier estimates, and the log-rank test was calculated. The significance level was set at 0.05. Statistical analyses were performed using R software version 3.6.3 (R Core Team) and SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Cohort characteristics

From Jan 1, 2002 to Dec 31, 2007, 4812 individuals had their first admission in a psychiatric bed available in the Ribeirão Preto catchment area. Information regarding date of birth or mother's name was not available in 793 records, which were excluded for not meeting the criteria required in the procedure of linkage to the death databases. Thus, 4019 patients were included in our sample (see Supplementary Table S2). The total number of person-years in the study's follow-up period was 42,720 (22,751 men and 19,969 women), and the median follow-up time of the cohort was 11.25 years. The median age of patients at first psychiatric admission was 35.00 years (interquartile range (IQR) 25.00–46.00). Eight hundred and three deaths (19.98%) were identified between Jan 01, 2002 and Dec 31, 2016, 560 in

Table 1 Characteristics of the cohort with first psychiatric admission from Jan 1, 2002 to Dec 31, 2007 and outcome of follow-up on Dec 31, 2016

	Women ($N=1818$)	Men ($N=2201$)	Total ($N=4019$)
Cohort characteristics			
Person-years of follow-up	19,969	22,751	42,720
Median years of follow-up (IQR)	11.42 (9.92–12.92)	11.17 (9.33–12.87)	11.25 (9.67–12.92)
Median age (IQR)	35.00 (25.00–46.00)	35.00 (26.00–46.00)	35.00 (25.00–46.00)
Vital status on Dec 31, 2016			
Dead	243	560	803
Median age of dead (IQR)	51.00 (40.50–64.00)	45.00 (35.00–58.00)	47.00 (36.00–60.00)
Median years of follow-up of dead (IQR)	5.67 (2.58–9.17)	5.00 (2.14–8.50)	5.08 (2.25–8.67)
Time after admission until death; *N* (%)			
0–5 years	121 (49.79)	267 (47.68)	388 (48.32)
5–10 years	83 (34.16)	208 (37.14)	291 (36.24)
10–15 years	39 (16.05)	85 (15.18)	124 (15.44)

IQR interquartile range

men and 243 in women. The median age of patients at death was 47.00 years (IQR 36.00–60.00) (Table 1).

The causes of death were divided into 18 categories (Table 2). Greater than 83% of deaths were related to natural causes, such as circulatory (19.18%), digestive (12.83%), and respiratory (12.70%) diseases. Patients admitted for alcohol-related disorders (F10) had a higher percentage of deaths related to diseases of the digestive system (K00–K95). In contrast, those admitted for nonalcohol psychoactive substance use (F11–F19) had deaths mainly related to external causes (V01–Y09), such as accidents, assaults and suicides. Psychotic disorders (F20–F29) had a higher percentage of deaths due to respiratory diseases (J00–J99), mood disorders (F30–F39) due to circulatory diseases (I00–I99), and other mental disorders (F00–F09 and F40–F99) due to endocrine, nutritional, metabolic (E00–E89) and neurological diseases (G00–G99).

Thirty-one (3.86%) suicides were recorded (MR = 72.50/100,000 person-years; SMR = 11.41 95% CI 9.19–14.11), 20 in men (MR = 87.93/100,000 person-years; SMR = 8.14, 95% CI 6.62–9.81) and 11 in women (MR = 55.11/100,000 person-years; SMR = 27.00, 95% CI 21.09–34.48). The median age was 39 years (men = 36.50 years and women = 41 years). Regarding the diagnosis at the first admission, suicides occurred in 11 (35.48%) patients with alcohol use disorders (F10), 7 (22.58%) with mood disorders (F30–F39), 5 (16.13%) with nonalcohol psychoactive substance use disorders (F11–F19), 4 (12.90%) with psychotic disorders (F20–F29), and 4 (12.90%) with other mental disorders (F00–F09 and F40–F99).

Mortality rates

Table 3 shows the overall mortality rates per 1000 person-years by sex and diagnosis. Overall, the risk of death was approximately three-fold (SMR = 2.90, 95% CI 2.71–3.11) in the general population with SMRs of 3.35 for men and 2.15 for women. The excess of mortality related to alcohol-related disorders (F10) was particularly high, i.e., increased five-fold compared with the rate for the reference population. Rates higher than expected were also observed for patients hospitalised due to the use of other psychoactive substances (F11–F19), psychotic disorders (F20–F29) and mood disorders (F30–F39).

The 803 deceased persons lost more than 22 thousand years of life; the average YLL was 27.64 years. The YLL for men was higher (27.87 years) than that for women (27.13 years). In the sample with nonalcohol psychoactive substance-related disorders, YLL was higher (39.22 years) than that noted in other mental disorders, and women lost more years of life (44.66 years) than men (38.33 years). The life expectancy at birth in this cohort was 47.27 years.

According to Kaplan–Meier curves (see Supplementary Figure S2), the survival of men in our cohort was significantly lower than that of women (log-rank test: $p<0.01$), and the survival of patients with alcohol-related disorders was significantly lower than that of patients with other diagnoses (log-rank test: $p<0.01$). During the 15-year follow-up, the survival of patients admitted for alcohol use disorders was 57%; it is expected that the half-life, i.e., the estimated time that only 50% of the patients remain alive, was 17.21 years after the first psychiatric admission.

Table 2 Causes of deaths in relation to the diagnosis at the first hospital admission by the International Classification of Diseases 10th version

Cause of death (ICD-10)	Diagnosis by ICD-10					
	F10	F11–F19	F20–F29	F30–F39	Others[a]	Total
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Natural						
Certain infectious and parasitic diseases (A00–B99)	21 (7.78)	7 (14.00)	6 (4.51)	14 (8.43)	11 (6.11)	59 (7.35)
Neoplasms (C00–D49)	29 (10.74)	4 (8.00)	12 (9.02)	15 (9.04)	19 (10.55)	79 (9.84)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	1 (0.37)	1 (2.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.25)
Endocrine, nutritional and metabolic diseases (E00–E89)	7 (2.59)	1 (2.00)	7 (5.26)	6 (3.61)	13 (7.22)	34 (4.23)
Mental, behavioural and neurodevelopmental disorders (F00–F99)	17 (6.30)	1 (2.00)	3 (2.26)	5 (3.01)	5 (2.78)	31 (3.86)
Diseases of the nervous system (G00–G99)	7 (2.59)	1 (2.00)	5 (3.76)	6 (3.61)	9 (5.00)	28 (3.49)
Diseases of the circulatory system (I00–I99)	42 (15.56)	6 (12.00)	24 (18.05)	42 (25.30)	39 (21.67)	154 (19.18)
Diseases of the respiratory system (J00–J99)	30 (11.11)	4 (8.00)	24 (18.05)	20 (12.05)	23 (12.77)	102 (12.70)
Diseases of the digestive system (K00–K95)	48 (17.78)	6 (12.00)	13 (9.77)	20 (12.05)	16 (8.89)	103 (12.83)
Diseases of the skin and subcutaneous tissue (L00–L99)	2 (0.74)	0 (0.00)	0 (0.00)	1 (0.60)	1 (0.56)	4 (0.50)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	1 (0.37)	1 (2.00)	1 (0.75)	0 (0.00)	0 (0.00)	4 (0.50)
Diseases of the genitourinary system (N00–N99)	8 (2.96)	2 (4.00)	6 (4.51)	3 (1.81)	3 (1.67)	23 (2.86)
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.60)	2 (1.11)	3 (0.37)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	18 (6.67)	2 (4.00)	5 (3.76)	9 (5.42)	9 (5.00)	43 (5.35)
Unnatural						
Accidents (V01–X59)	19 (7.04)	6 (12.00)	10 (7.52)	10 (6.02)	12 (6.67)	57 (7.10)
Suicide (X60–X84)	11 (4.07)	5 (10.00)	4 (3.01)	7 (4.22)	4 (2.22)	31 (3.86)
Assault (X85–Y09)	3 (1.11)	2 (4.00)	5 (3.76)	2 (1.20)	5 (2.78)	17 (2.12)
Other external causes of morbidity and mortality (Y10–Y98)	6 (2.22)	1 (2.00)	8 (6.01)	5 (3.01)	9 (5.00)	29 (3.61)
Total	270 (100.00)	50 (100.00)	133 (100.00)	166 (100.00)	180 (100.00)	803 (100.00)

[a]Others mental disorders = F00–F09 and F40–F99; Alcohol-related disorders = F10; Nonalcohol psychoactive substance use = F11–F19; Psychotic disorders = F20–F29; Mood disorders = F30–F39

Characteristics associated with a higher risk of death

In the univariate Cox regression analysis (Table 4), the risk of death was associated with sex ($p < 0.01$), age ($p < 0.01$), marital status ($p = 0.03$) and diagnosis ($p < 0.01$) at the first psychiatric admission. In a multivariate Cox regression analysis (Table 4) adjusted for all the variables (Model 1), mortality at the first psychiatric hospital admission was associated with sex ($p < 0.01$), age ($p < 0.01$), occupational status ($p = 0.02$) and diagnosis ($p < 0.01$). In model 2, a multivariate Cox regression analysis (Table 4) was adjusted exclusively for significant variables ($p < 0.05$), and higher mortality was associated with male sex (aHR = 1.62, 95% CI 1.37–1.92), age [20–39 years (aHR = 2.62, 95% CI 1.65–4.15), 40–59 years (aHR = 5.83, 95% CI 3.67–9.25) and ≥ 60 years (aHR = 21.47, 95% CI 13.48–34.17)], unemployment (aHR = 1.22, 95% CI 1.05–1.43), and diagnoses [alcohol-related disorders (aHR = 2.70, 95% CI 2.17–3.33), nonalcohol psychotics substance use (aHR = 1.79, 95% CI 1.27–2.53) and other mental disorders (aHR = 1.70, 95% CI 1.37–2.10)]. The proportional hazard assumption was analysed and confirmed. The global Schoenfeld test ($p = 0.42$) and visual inspection of curves log [-log (survival probability)] as a function of the follow-up time (in logarithmic scale) were considered (see Supplementary Figure S3). Cox regression models separately generated based on natural and unnatural causes of mortality are available in Supplementary Table S3.

Table 3 Mortality rates, standardised mortality ratios, excess mortality and years of life lost were reported in the cohort with the follow-up outcome in 2016

Diagnosis (ICD-10)	Sex	Person-year	MR (95% CI)	Deaths		Excess	SMR (95% CI)	YLL	Average YLL (95% CI)	Life expectancy (years)
				Observed	Expected	Mortality				
Alcohol-related disorders (F10)	Women	758	26.39 (16.57; 40.03)	20	4.07	15.93	4.91 (3.08; 7.45)	610.71	30.54 (26.27; 34.81)	47.98
	Men	6052	41.31 (36.42; 46.68)	250	44.59	205.41	5.60 (4.94; 6.33)	7,495.38	29.98 (28.84; 31.11)	41.32
	All	6810	39.65 (35.13; 44.59)	270	49.04	220.96	5.50 (4.87; 6.19)	8,106.09	30.02 (28.92; 31.12)	44.89
Nonalcohol psychoactive substance use (F11–F19)	Women	505	13.86 (6.06; 27.42)	7	2.84	4.16	2.46 (1.08; 4.87)	312.61	44.66 (34.25; 55.07)	33.86
	Men	2885	14.90 (10.92; 19.89)	43	21.26	21.74	2.02 (1.48; 2.70)	1,648.15	38.33 (34.66; 41.99)	32.97
	All	3390	14.75 (11.06; 19.29)	50	21.93	28.07	2.28 (1.71; 2.98)	1,960.76	39.22 (35.73; 42.71)	35.69
Psychotic disorders (F20–F29)	Women	3631	14.87 (11.28; 19.26)	54	20.47	33.53	2.64 (2.01; 3.41)	1,441.19	26.69 (24.02; 29.35)	51.83
	Men	5412	14.60 (11.63; 18.10)	79	39.88	39.12	1.98 (1.58; 2.46)	2,009.11	25.43 (22.74; 28.11)	45.87
	All	9043	14.71 (12.36; 17.37)	133	58.49	74.51	2.27 (1.91; 2.68)	3,450.30	25.94 (24.02; 27.86)	48.97
Mood disorders (F30–F39)	Women	9162	10.04 (8.14; 12.26)	92	51.65	40.35	1.78 (1.44; 2.17)	2,194.78	23.86 (21.45; 26.27)	54.66
	Men	4797	15.43 (12.20; 19.26)	74	35.35	38.65	2.09 (1.66; 2.61)	1,898.84	25.66 (22.64; 28.68)	45.64
	All	13,959	11.89 (10.18; 13.81)	166	90.29	75.71	1.84 (1.57; 2.13)	4,093.62	24.66 (22.78; 26.54)	50.25
Others mental disorders (F00–F09 and F40–F99)	Women	5913	11.84 (9.29; 14.87)	70	33.32	36.68	2.10 (1.65; 2.64)	2,033.87	29.06 (25.10; 33.02)	49.46
	Men	3605	31.62 (26.21; 37.84)	114	26.55	87.45	4.29 (3.55; 5.14)	2,557.37	22.43 (19.84; 25.02)	48.87
	All	9518	19.33 (16.69; 22.28)	184	61.54	122.46	2.99 (2.58; 3.44)	4,591.24	24.95 (22.71; 27.18)	49.96
All mental disorders (F00-F99)	Women	19,969	12.17 (10.71; 13.77)	243	113.17	129.83	2.15 (1.89; 2.43)	6,593.16	27.13 (25.42; 28.83)	51.39
	Men	22,751	24.61 (22.64; 26.72)	560	167.28	392.72	3.35 (3.08; 3.63)	15,608.85	27.87 (26.85; 28.89)	43.43
	All	42,720	18.80 (17.53; 20.13)	803	276.69	526.31	2.90 (2.71; 3.11)	22,202.01	27.64 (26.76; 28.52)	47.27

MR mortality rate per 1000 person-years; *SMR* standardised mortality ratio adjusted for sex and age; *YLL* years of life lost; life expectancy at birth in the state of São Paulo in 2010; *95% CI* 95% confidence interval; *ICD-10* International Classification of Diseases-10th revision

Table 4 Survival analyses for univariate and multivariate Cox regression models for the variables at the first admission from all causes of mortality

	Cohort ($N=4019$)	Death ($N=803$)	Crude	Model 1	Model 2
	N (%)	*N* (%)	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Sex					
Women	1818 (45.23)	243 (30.26)	1.00	1.00	1.00
Men	2201 (54.77)	560 (69.74)	2.01 (**1.73; 2.34**)	1.95 (**1.66; 2.28**)	1.62 (**1.37; 1.92**)
Age group					
< 20 years	439 (10.92)	20 (2.49)	1.00	1.00	1.00
20–39 years	1990 (49.52)	245 (30.51)	2.82 (**1.79; 4.45**)	3.00 (**1.87; 4.82**)	2.62 (**1.65; 4.15**)
40–59 years	1279 (31.82)	334 (41.59)	6.48 (**4.13; 10.18**)	7.06 (**4.40; 11.32**)	5.83 (**3.67; 9.25**)
≥ 60 years	311 (7.74)	204 (25.41)	21.10 (**13.33; 33.41**)	21.90 (**13.58; 35.33**)	21.47 (**13.48; 34.17**)
Occupational status					
Employed/homemaker/student	1271 (31.62)	245 (30.51)	1.00	1.00	1.00
Unemployed	2748 (68.38)	558 (69.49)	1.04 (0.89; 1.21)	1.20 (**1.03; 1.41**)	1.22 (**1.05; 1.43**)
Marital status					
Single/divorced/widowed	2606 (64.84)	480 (59.78)	1.00	1.00	–
Married/partnered	1413 (35.16)	323 (40.22)	1.29 (**1.12; 1.49**)	0.97 (0.84; 1.13)	–
Hospital service					
Psychiatric hospital	1089 (27.09)	226 (28.15)	1.00	1.00	–
Emergency unit	2092 (52.05)	417 (51.93)	1.00 (0.85; 1.17)	1.19 (0.93; 1.54)	–
General hospital	838 (20.86)	160 (19.92)	0.90 (0.74; 1.11)	1.04 (0.84; 1.29)	–
Year of admission					
2002	610 (15.18)	157 (19.55)	1.00	1.00	–
2003	629 (15.65)	139 (17.31)	0.88 (0.70; 1.10)	0.82 (0.65; 1.03)	–
2004	779 (19.39)	154 (19.18)	0.81 (0.65; 1.01)	0.82 (0.65; 1.04)	–
2005	709 (17.64)	125 (15.57)	0.78 (**0.61; 0.99**)	0.75 (**0.59; 0.96**)	–
2006	675 (16.79)	118 (14.69)	0.85 (0.66; 1.08)	0.89 (0.69; 1.14)	-
2007	617 (15.35)	110 (13.70)	0.93 (0.72; 1.19)	1.04 (0.80; 1.35)	-
Length of stay					
1–2 days	1999 (49.75)	366 (45.58)	1.00	1.00	-
3–10 days	1064 (26.47)	240 (29.89)	1.23 (**1.04; 1.45**)	1.18 (0.99; 1.40)	-
11–30 days	652 (16.22)	136 (16.94)	1.09 (0.89; 1.33)	1.06 (0.86; 1.32)	-
31 days or more	304 (7.56)	61 (7.59)	1.06 (0.81; 1.39)	1.01 (0.76; 1.34)	-
Origin					
Other municipalities	1850 (46.03)	347 (43.21)	1.00	1.00	-
Ribeirão Preto	2169 (53.97)	456 (56.79)	1.12 (0.97; 1.29)	1.06 (0.91; 1.22)	-
Diagnosis (ICD-10)					
Mood disorders (F30–F39)	1263 (31.43)	166 (20.67)	1.00	1.00	1.00
Psychotic disorders (F20–F29)	823 (20.48)	133 (16.56)	1.24 (0.98; 1.55)	1.27 (**1.01; 1.62**)	1.29 (**1.02; 1.63**)
Nonalcohol psychoactive substance use (F11–F19)	319 (7.94)	50 (6.23)	1.26 (0.92; 1.73)	1.98 (**1.39; 2.82**)	1.79 (**1.27; 2.53**)
Alcohol-related disorders (F10)	714 (17.76)	270 (33.62)	3.36 (**2.77; 4.08**)	2.76 (**2.21; 3.45**)	2.70 (**2.17; 3.33**)
Others mental disorders[a]	900 (22.39)	184 (22.92)	1.62 (**1.32; 2.00**)	1.78 (**1.44; 2.22**)	1.70 (**1.37; 2.10**)

HR hazard ratio; *aHR* adjusted hazard ratio; model 1 include sex, age, occupational status, marital status, hospital service, year of admission, length of stay, origin and diagnosis; model 2 include sex, age, occupational status and diagnosis; *95% CI* 95% confidence interval; Bold significant values; *ICD-10* International Classification of Diseases-10th revision

[a]Others mental disorders = F00–F09 and F40–F99

Table 5 Association of natural and unnatural causes of mortality for death certificate variables

	Natural ($N=669$) N (%)	Unnatural ($N=134$) N (%)	p value
Sex			0.20
Women	206 (30.79)	37 (27.61)	
Men	463 (69.21)	97 (72.39)	
Age group at death			**< 0.01**
16–39 years	103 (15.39)	55 (41.04)	
40–59 years	307 (45.89)	58 (43.29)	
≥ 60 years	259 (38.72)	21 (15.67)	
Skin colour			**0.03**
White	506 (75.63)	90 (67.16)	
Nonwhite	163 (24.37)	44 (32.84)	
Marital status at death			0.08
Married/partnered	190 (28.40)	28 (20.89)	
Single/divorced/widowed	479 (71.60)	106 (79.11)	
Municipality of death			0.50
Ribeirão Preto	350 (52.32)	65 (48.51)	
Other municipalities	319 (47.68)	69 (51.49)	
Diagnosis (ICD-10) in first admission			**0.01**
Mood disorders (F30–F39)	142 (21.22)	24 (17.91)	
Psychotic disorders (F20–F29)	106 (15.85)	27 (20.15)	
Nonalcohol psychoactive substance use (F11–F19)	36 (5.38)	14 (10.45)	
Alcohol-related disorders (F10)	231 (34.53)	39 (29.10)	
Others mental disorders (F00–F09 and F40–F99)	154 (23.02)	30 (22.39)	

p value = Chi-squared test; Bold significant values

ICD-10 International Classification of Diseases-10th revision

The 803 deaths were categorised into natural causes ($N=669$; 83.3%; A00–R99) and unnatural causes ($N=134$; 16.7%; V01–Y98). In Table 5, unnatural causes of mortality were associated ($p<0.01$) with age 16–39 years (41.04%), whereas natural causes are associated with the age of 60 years or older (38.72%). Although 74% of deaths occurred in patients with white skin colour, nonwhite patients died more often due to unnatural (32.84%) than natural (24.37%) causes ($p=0.03$). Moreover, the diagnosis of nonalcohol psychoactive substance disorders at the first psychiatric admission increased the number of deaths by unnatural causes.

Sensitivity analysis

We used five cycles of multiple imputations via MICE. The multiple imputations used did not influence our results (see Supplementary Table S4); it only maximised the sample size, without directly influencing the results. The rate ratios of the sensitivity analysis were virtually the same throughout the study period compared to the initial results.

Discussion

To the best of our knowledge, this is the first study performed in Latin America aiming to analyse the mortality of individuals after their first psychiatric admission, considering a wide range of diagnoses. Our results confirmed that people admitted to hospitals in the early stages of a psychiatric condition have an approximately three-fold greater risk of death than the general population, reducing the life expectancy by more than 27 years. Excess mortality was observed in all the diagnoses with a higher impact from alcohol and other psychoactive substance-related problems. We also observed that some sociodemographic features, such as sex and unemployment at the admission, may be associated with excess mortality in psychiatric patients.

The mortality rate in patients with mental disorders was 2.90-fold greater than that in the general population with an SMR ranging from 1.84 (95% CI 1.57–2.13) for mood disorders (F30–F39) to 5.50 (95% CI 4.87–6.19) for alcohol-related disorders (F10). All diagnoses were also associated with a shorter life expectancy with excess YLLs ranging from 24.66 for mood disorders to 39.22 for nonalcohol psychoactive substance use disorders. The pattern of overall excess mortality observed in our study is consistent with

previous studies. However, the values were greater than those previously reported, mainly in HICs, which have a death risk of 2.22 and 10 YLLs [1]. Similarly, psychotic disorders were responsible for 25.94 (95% CI 24.02–27.86) YLLs in our study. This value was much higher than that reported in a systematic review [22] that covered all inhabited continents, except South America, where schizophrenia had a mean weight of 14.50 YLLs. This is a highly worrisome finding, considering that life expectancy at birth in LMICs is 13 years less than that in HICs (70.10 *vs.* 83.70) [23]. Several reasons can explain these discrepancies, such as social, political, and economic inequalities, urban violence and high suicide rates [24].

Our data are also consistent with previous studies indicating a reduction of more than 20 years in life expectancy in patients with alcohol use disorders [8, 9, 25]. However, we observed excess mortality in people with alcohol use disorders of greater than five times, which is higher than the values found in previous reports [26]. We also observed that the excess mortality from alcohol-related disorders was higher in men (SMR = 5.60, 95% CI 4.94–6.33) than in women (SMR = 4.91, 95% CI 3.08–7.45). This finding contrasts with the results of a meta-analysis [26] of 81 studies (mainly HICs), showing a greater risk of death for women (RR = 4.57, 95% CI 3.86–5.42) than men (RR = 3.38, 95% CI 2.98–3.84). A possible explanation is that in Brazil, the prevalence of heavy drinking is significantly lower in women than in men [27]. Thus, Brazilian women would be less likely to engage in problem drinking, develop alcohol-related disorders or alcohol withdrawal symptoms [28], and, as a consequence, have fewer health complications due to alcohol use.

We found a relatively low mortality rate in mood disorder patients (SMR = 1.84, 95% CI 1.57–2.13). This result differs from the only Brazilian study [19] conducted over 25 years ago, where excess mortality was concentrated in psychotic women who also presented depressive symptoms. This change over time has been previously reported [8, 29, 30] probably due to a reduction in social stigma on depression, which may have increased the treatment-seeking behaviour. In addition to a rapid diagnosis, adherence to drug treatment and monitoring by the mental health team may also have contributed to reducing mortality rates.

In general, more mortality due to unnatural causes was noted in patients who were admitted for disorders related to nonalcohol psychoactive substance use. This increase in mortality may be related to a higher risk of accidents with motor vehicles, the use of weapons and involvement in physical aggression and violence commonly associated with psychoactive substance use [31–33].

Notably, the mortality of psychiatric patients due to natural causes also remained higher than that of the reference population. Some studies attribute this increase in the association of schizophrenia with cardiovascular diseases [34, 35], depressive and neurotic disorders with gastrointestinal causes [5] and substance use disorders with liver diseases [36], highlighting the need for risk reduction, especially for these diseases. Excess mortality in patients with mental disorders has been associated with modifiable unhealthy lifestyles (e.g., smoking, poor diet, physical inactivity, alcohol use or drug use), which cause significant harm to health [35, 37, 38].

Our data also indicated that the highest excess mortality of psychiatric patients admitted for the first time occurred mainly in the first year after hospital admission, and approximately half of these deaths occurred less than 5 years after the first admission. Previous studies [39, 40] also reported that the highest mortality rate for psychiatric patients occurred in the first year after admission, especially deaths related to suicide [11, 39–41].

Although suicide mortality rates in our cohort have an SMR that is greater than 11 times higher than the rate for the Ribeirão Preto catchment area, our rates (72.50/100,000 person-years) were not as high as those reported in other studies (484.00/100,000 person-years) that integrated a meta-analysis [11] that investigated the suicide rate after discharge from psychiatric hospitalisation. This can be explained, at least partially, by the fact that Brazil is a country with strong religious beliefs since religiosity contributes as a protective factor in suicidal behaviour [42].

Our study also identified that individuals with nonwhite skin colour are more vulnerable to death from unnatural causes. This result differs from studies in HICs [43], showing higher mortality rates from unnatural causes in people with white skin colour. In Brazil, the excess of mortality due to unnatural causes in nonwhite skin colour may be related to the effects of inequalities, social disadvantages and discrimination [44, 45]. This information may help to develop targeted public health strategies in the future, but more in-depth studies in LMICs are needed.

Strengths and limitations of the study

Our results should be considered given several limitations. First, the number of deaths may still be higher than what we reported. Our hospital admission data were linked in the databases of the SEADE Foundation (State data analysis system of São Paulo), which records only deaths that occurred in the state of São Paulo. We know that patients are mobile, and there may be deaths that occurred in other Brazilian states, which were not registered in our system. However, it does not diminish our findings since the mortality rates found are substantially large, highlighting the need for actions that must be taken to minimise them. Second, although our results can support a causal relationship

between the diagnosis of mental disorders and mortality, caution is needed when interpreting these associations. Associations can also have a noncausal origin and result from confusion. Third, comorbidities and socioeconomic status are important potential confounding factors [38], which were not adjusted in this study due to a lack of information in the records. Fourth, difficulty in comparing the SMR with other countries with different age compositions and not standardised by the same reference population. Fifth, the number of patients included in our sample is not very large, and our results cover a single catchment area. Sixth, the study is also affected by possible errors and omissions that may exist in the databases, and data for some of the analysed variables are lacking.

Although our results need to be interpreted in the context of some limitations, our study is one of the few to assess associations between first psychiatric hospital admission, mortality and several psychiatric diagnoses. This is a strong point of our study because previous studies did not examine in detail the excess of alcohol-related mortality but the disorders due to substance use in general. Our study also contributes to the literature by exploring trends in excess mortality in a Brazilian cohort, using a population-based dataset covering a long period. In addition, these findings contribute substantially to a significant information gap from years of life lost in South America. Few studies have examined the mortality of psychiatric patients in population cohorts, especially in LMICs.

Conclusion

The excess mortality reported in our study suggests that the first psychiatric hospitalisation reduces the life expectancy of people with mental disorders by 2–4 decades. Most patients died from potentially treatable diseases. Patients with severe mental disorders, especially those related to the use of alcohol and other psychoactive substances, should be a priority in preventive actions aimed at health. The study highlights the need for a broad and intensive follow-up in mental health services, adherence to treatment, and improvement of the patients' physical health since the early stages of mental disorders.

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Author contributions CMD-B and PRM conceived the study. DLR, PRM and CMD-B contributed to the study design. PRM and CMD-B obtained funding. REMB, DLR and MGR collected the cohort data. LCCM, CECF and BCW collected the death data. DLR analysed the data. All authors collaborated in the interpretation of the data. DLR wrote the first draft of the manuscript. CMD-B and PRM critically revised the manuscript. All the authors read and approved the final version of the manuscript.

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Data availability Data or any additional information is available upon request from the authors.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

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