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Adjusted mortality rates attributable to Alzheimer's disease dementia, Brazil, 2009-2013

Tasas corregidas de mortalidad atribuible a la demencia por la enfermedad de Alzheimer, Brasil, 2009-2013

Taxas corrigidas de mortalidade atribuíveis à demência pela doença de Alzheimer, Brasil, 2009-2013

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Abstract

This paper provides estimates of mortality rates from Alzheimer's disease dementia (AD) in the elderly Brazilian population. Data were obtained from the 2010 Population Census *by Brazilian Institute of Geography and Statistics (IBGE) and microdata on mortality in Brazil's 27 state capitals recorded in the Brazilian Mortality Information System (SIM) for the population 65 years or older by place of residence for the years 2009 to 2013. Corrections were obtained for underreporting of mortality, and final adjustments were made to the specific mortality rates based on Bayesian methods with prior probability distributions built on the basis of information obtained from a meta-analysis. The mortality rates from all dementias and from AD in Brazil were higher than in developed countries. The mortality rates from Alzheimer's disease in 2013 were 140.03 (95%CI: 117.05; 166.4) and 127.07 (95%CI: 103.74; 149.62) per 100,000 inhabitants, respectively, in men and women. The contribution of AD to mortality in elderly Brazilians was 4.4% (95%CI: 3.25; 5.72) in the group with 0 to 3 years of schooling, independently of age and sex. The study aimed to increase knowledge on corrected estimates of mortality rates from Alzheimer's disease based on vital statistics, providing more precise and pertinent evidence-based estimates.*

Dementia; Alzheimer Disease; Mortality; Bayes Analysis; Meta-analysis

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Introduction

The demographic transition is a process that involves changes from high to low fertility and mortality rates. One of the main consequences is the decrease in the young population and a steady increase in the population 65 years or older [1,2,3,4]. In addition to accelerated population aging, the demographic transition is accompanied by a change in mortality patterns in various stages of the epidemiological transition, leading to the increase or emergence of new diseases in the elderly [5,6,7,8]. One such disease that merits special attention is dementia.

Dementia is a generic term to classify a set of diseases that affect the elderly population. Dementia from Alzheimer's disease (AD) is the most frequent [7,9,10], accounting for 60% of all dementia cases in the world [11,12,13]. AD is currently acknowledged as a growing global public health problem [14,15,16], and its presence in elderly individuals greatly increases the risk of death [17].

Ferri et al. [15] reported that in the year 2004, at least 24 million individuals had some kind of dementia around the world. In developing countries, it is suspected that at least 60% of the elderly suffer from dementia. This proportion may reach 71% by the year 2040 [18,19,20], potentially affecting 81 million individuals [15]. According to Wimo et al. [18], a significant share of individuals with dementia live in developing countries.

The interest in studying AD has grown in Latin America and the Caribbean in recent years [15,20,21,22]. Nevertheless, the results of these studies vary considerably, especially regarding the AD prevalence in Latin America and the Caribbean. In some countries the prevalence estimates are lower than the ones observed in developed countries [18,23].

There are also difficulties in obtaining reliable estimates for the mortality rates from AD. This is due to recording as problems in vital statistics systems, leading mainly to errors in age, death records, missing information, diagnostic errors, difficulties in access to health services by the elderly population, etc. [24,25,26]. Studies on mortality from AD are thus a major challenge, since vital statistics records are the main source of information.

Our main objective is to generate adjusted estimates of mortality attributable to AD in the elderly population of the 27 Brazilian state capitals, from 2009 to 2013. Initially we provide estimates for the mortality rates from all types of dementia, based on which we obtained estimates for the specific mortality rates from AD.

Materials and methods

The study used microdata from the mortality records in Brazilian Mortality Information System (SIM; http://www.datasus.gov.br) for the 27 Brazilian state capitals, by place of residence, for the years 2009-2013. The definition of mortality from all types of dementia was based on the 10th revision of International Classification of Diseases (ICD-10). More data can be found at https://github.com/jjsandoval/ArticuloCSP.

Inclusion criteria

Deaths from dementia according to direct cause of death, 1st, 2nd, and 3rd causes that preceded death (lines A-D), and important causes of disease I and II, recorded in the vital statistics, via the search for codes G30.0–G30.9, with F00-F09 as excluded events.

Exclusion criteria

Mortality due to mental or behavioral disorders recorded as codes F1, for example, deaths caused by alcoholism, opioids, and other drugs, both avoidable and unavoidable, deaths classified as R99 (other ill-defined/unspecified causes, but recorded by physicians), and R98, deaths unattended by physicians. In addition, previous studies found few cases of age-related physical disability associated with dementia, so deaths from this cause (code R54) were excluded, totaling 3,084 cases in the study period.

Variables

For the case count, the variable $I(x)$ was constructed, assigning 1 to death attributable to dementia and 0 otherwise. The rates' denominator was obtained from the 2010 *Brazilian Population Census*, extracted from Integrate Public Use Microdata Series (IPUMS. https://international.ipums.org/international/index.shtml, accessed on 08/Sep/2015) , for the 27 state capitals. Data related to year 2010 were projected to July 1st (half of the period). For the years 2009 and 2011-2013, population projections were performed, based on information from the national census of 2000 and 2010. The count $I(x)$ allowed obtaining the numerator for the mortality rates from dementia for each of the mortality lines in the microdata. Cases were extracted from the SIM database via an alphanumeric search using the ICD-10 codes, with the *grepl* function from the R software (https://www.r-project.org/).

Categories for variables sex and age coincide between the SIM and the 2010 census. For variable education however, SIM assumes categories: 0-3, 4-7, 8-11, and 12 or more years of schooling, and the census assumes different caterories. We thus performed an approximate construction using the edattaind code in IPUMS. The independent variables were: sex (1 = male, 2 = female), age (1 = 65-69, 2 = 70-74, 3 = 75-79, 4 = 80-84, and 5 = 85 years or older), education (1 = 0-3, 2 = 4-7, 3 = 8-11, and 4 = 12 or more years of schooling), and period (1 = 2009, 2 = 2010, 3 = 2011, 4 = 2012, and 5 = 2013).

The proportion of missing data was 0.5% for sex and 18.9% for years of schooling in the SIM. In the 2010 census, the proportions were 14.47% for years of schooling and one missing for sex.

For imputation of missing data, we assume "randomness" of the sample by sex and proceeded according to the tendencies shown in the mode (Bernoulli process). For education, we assume missing not at random (MNAR) and fit a Bayesian model, considering education (1 = 0, 2 = 1-3, 3 = 4-7, 4 = 8-11, and 5 = 12 or more years of schooling) as an ordinal response, dependent on age and sex. A multinomial response is assumed with parameters p_{ij}, $i = 1, 2,\ldots, N$ and $j = 1,2,3,4,5$, depending on: g_1, g_2, g_3, g_4, normality is assumed in g_1 and inverse gamma distributions are assumed for the other g's. The *a priori* parameters elicitation were obtained from the 2010 census, where 25% of the population 65 years or older had no formal education, 50% had from 1 to 3 years, 11% from 4 to 7, 7% from 8 to 11, and 7% more than 12 years of schooling. For further details on the parameters, see Sandoval [27].

In addition, corrections were performed for coverage based on the estimates provided by Queiroz et al. [28] which are calculated for the deaths in Brazilian state capitals for ages 15 to 60 years. Among the estimates presented by Queiroz et al. [28], we considered those produced with the adjusted synthetic extinct generations method (SEG-adj) proposed by Bennett & Horiuchi [29] and corrected by Hill et al. [30], as it they are based on more flexible assumptions. However, this method only allows initial corrections to the data, since it has limitations that will be discussed in the last section of this paper. These limitations inspired us to use Bayesian models to improve the fits of the rates, as described next.

Without correction for coverage and imputation of missing data, there were only 38,657 dementia cases (4.96% of the total) from 2009 to 2013. With correction for coverage, the total was 42,831 cases (5.5%), and with imputation of missing data [27] total increase to 51,307 deaths (6.58%), higher than usually found in SIM sources.

Bayesian model construction

The target response variable Y_j was the proportion of deaths attributable to all types of dementia, obtained by cross-analyzing the independent variables with the microdata base according to $I(x)$, in a total of N = 200 subpopulations (contingency table).

Let us assume the selection of a random sample in each subpopulation defined by the covariables sex, age, year, and education, that is, $j = \{\text{sex, age, year, education}\}$ y j: 1, 2,… , N. Let y_j be the observed proportion of deaths from all types of dementia in the subpopulation j among the Nj individuals exposed to the risk. The dependence between Y_j and the independent variables was modeled by the expected value of Y_j, given a random effect V_j, denoted by $E(Y_j|V_j = v_j)$, generalized, from Dobson & Barnett [31] as:

$$E(Y_j|V_j = \upsilon_j) = \mu_j\upsilon_j = N_j\theta_j\upsilon_j \qquad (1)$$

We assume that where $\theta_j = \exp(\beta_0 + \sum_{k=1}^{p} \beta_k X_{kj})$ where θ_j, $0 \leq \theta_j \leq 1$, is the mortality rate for all types of dementia within the j-th subpopulation. The random effect V_j is included into the model to account for the existence of overdispersion into Y_j, assume that Vj has a gamma distribution $G(r_j, r_j/\mu_j)$. For the parameter r_j, we consider, an inverse gamma prior distribution with fixed hyperparameters $a > 0$ and $b > 0$, which is non-informative. The rate θ_j is defined as:

$$\theta_j = \frac{r_j}{r_j + \mu_j}, j = 1, 2, \ldots, N \quad (2)$$

Where $E(Y_j) = \theta_j N_j = \mu_j$ and N is the total number of independent subpopulations in the contingency table. One can demostrate [27] that the unconditional marginal distribution of Y_j, in the mixed distribution of Y_j and V_j, is a negative binomial distribution.

For the Bayesian model (1), the model definition is completed by specifying the distributions of the regression parameters β_k, $k = 0, 1, \ldots, p$. Such prior distributions are informative distributions which the mean and variance are specified based on information sources obtained from a meta-analysis. To complete the specification of the Bayesian model in (1), centered normal prior distributions with precision 1.0 x 10^6 for β_0 and for the effects of the study period. For the effects of sex, age groups, and schooling, informative prior distributions are assumed for β_k, where the mean and variance are defined from extra information obtained from a meta-analysis. In addition, for these effects, since the exploratory results of the β_k combined in the meta-analysis were unimodal and approximately symmetrical, and as recommended by Gelman et al. [32], we assumed normal prior distribution as described below.

The information from a meta-analysis was obtained by a search of more than 2,000 articles in the MEDLINE and SciELO bases from 2000 to 2016. Among these, 15 studies [21,33,34,35,36,37,38,39,40,41,42,43,44,45,46] satisfied the criteria for the meta-analysis. The selected articles were original studies that included information on the risk factors associated with dementia. Selection was based on the diagnostic criteria for "dementia", "dementia not otherwise specified", "education" and "dementia", "sex and dementia", "dementia and age", "prevalence", "risk factors", and "epidemiology", excluding studies that used any other term that did not allow comparison with the others.

Informative hyperparameters were obtained from prior available information about risk factors for dementia. In particular, estimates of the odds ratios (OR) by education and relative risks (RR) by sex and age groups were used for this purpose.

For the effect of sex, a normal prior distribution with a mean of -0.01 and standard deviation (SD) of 0.114 is assumed; for the effects of age groups, normal distributions were obtained with means and SDs given, respectively, by: 0.833 and 0.141 (group 70-74 years), 1.56 and 0.141 (group 75-79), 2.21 and 0.138 (group 80-84), and 2.59 and 0.289 (group 85 years or older); for the effect of schooling, normal prior distributions were considered with means and SDs, given, respectively by: 1.09 and 0.253 (group with no schooling), 0.95 and 0.253 (1-3 years), 0.84 and 0.084 (4-7 years), and 0.37 and 0.084 (8-11 years of schooling) [27].

Model (1) is known as a Bayesian log-linear regression model [47]. Processing and analysis of the information required MCMC simulation methods and was performed, using the R and JAGS software (http://mcmc-jags.sourceforge.net/). The following results were based on estimates of θ_j, specific mortality rates (SMR), using 95% highest posterior density (HPD) credible intervals (CI) and the *a posteriori* median in all types of dementia. According to the estimates previously obtained by meta-analysis, the proportion of AD was 72% (95%CI: 58.9; 84.7) of all dementias [27].

Results

Table 1 shows the estimated specific mortality rates. Mortality for men was 10% higher than in women, but without statistical significance. For all dementias, there was an increase of 9.5% in the mortality rate 70-74-year group, if compared to the 65-69-year group. This contribution increases considerably with age, such that in the group 85 or older, it is 84% higher than in the youngest group. For education, the contribution was 6% in the group with 0-3 years of schooling if compared to such group with 12 years or more. For AD, the contribution was only 4.4%, however it was twice higher on

Table 1

Estimates of population attributable risk (PAR%) based on mortality rate ratios (RR) for dementia and Alzheimer's disease dementia (AD). Negative binomial Bayesian regression model with prior information vía meta-analysis. Brazil, 2009-2013.

Variables/Parameters	RR = Exp(β)	All dementias		AD	
		PAR%	95%CI	PAR%	95%CI
Gender					
Male	1.10	0.83	-0.02; 1.60	0.60	-0.02; 1.16
Age (years)					
70-74	2.32	9.51	7.37; 11.78	7.04	5.42; 8.77
75-79	7.32	33.54	29.77; 37.47	26.65	23.38; 30.14
80-84	17.96	57.53	53.48; 61.24	49.38	45.29; 53.21
85 o más	64.64	83.57	81.28; 85.78	78.55	75.77; 81.29
Education (years of study)					
0-3	1.80	6.01	4.46; 7.78	4.40	3.25; 5.72
4-7	1.19	1.49	0.29; 2.82	1.08	0.21; 2.05
8-11	1.40	3.13	2.07; 4.33	2.27	1.50; 3.15

95%CI: 95% confidence interval.

Reference category: gender – female, age – 65-69 years, schooling – ≥ 12 years of study. Prevalence of dementia in the exposed population: 7.99% and AD: 5.75%.

Source: estimates based on microdata from Brazilian Mortality Information System (SIM) and 2010 *Brazilian Population Census*.

average, than in the other schooling groups.

For identification of trends by age and schooling, a graphic for the logarithm of AD-specific mortality rates for men and women is presented (Figure 1). Figure 1a shows the highest SMRs in the groups with the lowest education level (less than 7 years) in all the age groups. From 4 to 11 years of education, the SMR logarithm was similarly stable. However, the trends in the SMR across all the age groups decay similarly, from the lowest level (0-3 years) to the highest level of formal education (12 years or more).

Figure 1b shows a high increase in the rates as the ages increase for in all the schooling levels. The specific mortality rates are also statistically higher in individuals with less formal education (0-3 years) than in the other groups, according to the HPD CIs. Two major groups were clearly distinguished: the group with 0-3 years of schooling and the joint group, whitall indivuduals with higher education (Figure 1b).

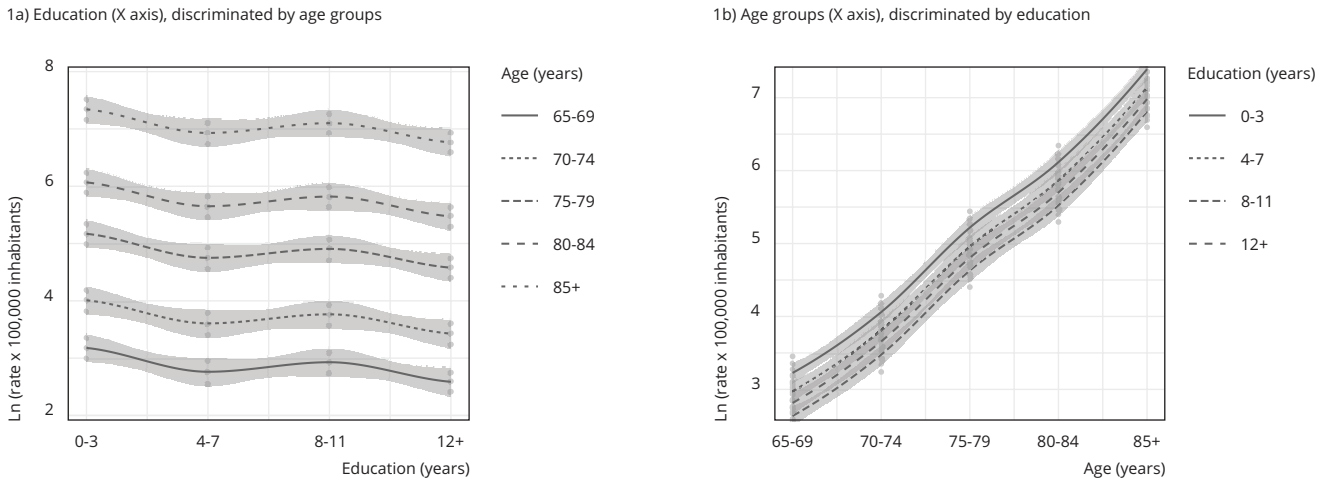
Table 2 again features for the differences in SMR by age groups at each level of education. For example, the 65-69-year age group, the SMR from AD is 24.05 (95%CI: 20.06; 28.67) for every 100,000 women with 3 years or less of formal education. For individuals with 4-7 years of education, the Alzheimer SMR was 15.88 (95%CI: 12.89; 19.37). The SMR showed a slight increase for 8-11 years of education (18.82; 95%CI: 15.59; 22.32), but it is not significantly different from the previous level, and decreased until reaching 13.42 (95%CI: 11.2; 15.62) in the group with 12 years or more of schooling. There were no differences in the HPD CI for the mortality rates of of education groups. The opposite is observed for the group with 0-3 years of education (Figure 1b).

Analogous results were obtained with population 85 years or older, except for those indiviuals with 12 years or more of schooling, showing some statistical differences at some levels of education.

Tables 3 and 4 show the regional results. The sex-adjusted estimates for SMR were not statistically significant, as already observed in the overall results. The medians were similar and the confidence intervals overlapped. For the North of Brazil, we analyzed the cities of Porto Velho (Rondônia State), Manaus (Amazonas State), and Rio Branco (Acre State). Results for the city of Porto Velho should be highlight as because it had the lowest estimates in the region from 2009 and 2013, ranging from 5.5 to 9.9 deaths per 100,000 inhabitants (Table 3). The 95%CI indicated high posterior variability and

Figure 1

Logarithm of specific mortality rates attributable to Alzheimer's disease in men and women, by age, gender, and schooling, for Brazil, 2013.



no significant differences between the SMR in the 65-69 age group, when comparing the three cities. Posterior distributions of SMR in women with 85 years or older in Porto Velho, displayed wide dispersion with a median of 94.7 (95%CI: 26.5; 203.1) for 2009 and 169.2 (95%CI: 64.3; 344.4) for 2013 in Porto Velho. For the city of Río Branco, the rates were nearly double of those obteined for the other two cities, and there were no statistical differences when comparing the respective age groups.

In the Northeast, we selected the cities of Salvador (Bahia State), Recife (Pernambuco State), São Luís (Maranhão State), and Natal (Rio Grande do Norte State). There was an increase in the SMR if compared to the SMR cities in the North of Brazil. The estimates SMR were very close to those obtained for the city of Río Branco, for example. Importantly, the HPD intervals showed less variation in this region, indicating greater precision in the SMR estimates if compared to the ones obtained for state capitals in the North. However, there were no statistically significant differences by age or years of schooling.

In the Central region, we selected the cities of Cuiabá (Mato Grosso State), Goiânia (Goiás State), and Campo Grande (Mato Grosso do Sul State). The SMR estimates in the region reduced to approximately half of those in the North. However, there were no statistically significant differences at 95%. It is noteworthy that the city of Brasília also displayed similar rates to the posterior median for cities in the Central region.

The Southeast and South regions of Brazil presented the best vital statistics. The Southeast also showed highest SMR in individuals 85 or older, among all the populations analyzed. The posterior variations of the HPD CI, by year and all the cities, were also much smaller than that obtained in the other regions.

Discussion

In this study, we provide adjusted mortality estimates from Alzheimer's disease in Brazil, for the years 2009 to 2013, by combining the rigorous search for cases attributable to dementia with indirect estimation methods. We hope our results are useful for the public health sector and can also call attention to the importance of examining data errors in the vital statistics of developing countries, such as recommended by Luy [48]. However, there are significant limitations to our study.

Table 2

Estimates of specific mortality rates (SMR per 100,000 inhabitants) from Alzheimer's disease for the year 2013, by educational level, age, and gender, based on the results of the negative binomial Bayesian regression model with prior probability built via meta-analysis.

Education (years of study)/ Age (years)	Men		Women	
	Median	95%CI	Median	95%CI
0-3				
65-69	26.45	22.03; 31.60	24.05	20.06; 28.67
70-74	61.33	51.03; 72.57	55.72	45.64; 65.81
75-79	194.53	162.18; 230.87	176.15	147.33; 209.66
80-84	476.73	396.62; 568.57	432.7	362.48; 511.76
85 or older	1,710.47	1.410.05; 2.044.79	1,555.48	1,287.47; 1,838.29
Total	194.53	162.18; 230.87	176.15	147.33; 209.66
4-7				
65-69	17.48	14.42; 21.54	15.88	12.89; 19.37
70-74	40.48	34.11; 49.25	36.72	30.40; 44.77
75-79	128.32	108.09; 153.47	116.30	95.83; 138.74
80-84	314.14	260.59; 378.41	284.80	236.57; 341.93
85 or older	1,131.46	936.94; 1,362.32	1,027.31	846.04; 1,228.58
Total	128.32	108.09; 153.47	116.30	95.83; 138.74
8-11				
65-69	20.70	17.17; 54.51	18.82	15.59; 22.32
70-74	47.88	39.82; 56.37	43.49	35.84; 51.55
75-79	151.73	126.01; 179.33	137.83	111.64; 160.50
80-84	372.82	310.82; 442.04	337.82	283.03; 399.48
85 or older	1,337.86	1,102.7; 1.572.82	1,215.32	1,023.86; 1,435.13
Total	151.73	126.01; 179.33	137.83	111.64; 160.50
12 or more				
65-69	14.75	12.42; 17.20	13.42	11.20; 15.62
70-74	34.16	28.52; 40.25	31.04	25.52; 36.86
75-79	108.22	90.96; 127.55	98.14	81.68; 115.15
80-84	264.88	221.77; 312.74	241.15	199.49; 280.69
85 or older	954.68	806.22; 1.129.06	866.86	730.80; 1,025.40
Total	108.22	90.96; 127.55	98.14	81.68; 115.15
Total	140.03	117.05; 166.40	127.07	103.74; 140.62

95%CI: 95% confidence interval.

Note: the proportion of Alzheimer's disease out of all demetias was estimated via meta-analysis.

Source: estimates based on microdata from Brazilian Mortality Information System (SIM) and 2010 *Brazilian Population Census*.

First, our work is limited to mortality data for the state capitals in Brazil. Therefore, it is not representative of the whole country. We restrict the analysis to state capitals hoping to reduce the loss of information due to the underreporting of deaths, that usually are more prevalent in the less developed areas. However, we had to use correction factors for the under-registration of deaths that are specific for the entire state populations, all causes of death, ages 15 to 60, provided by Queiroz et al. [28]. So, we had to assume that the same factors apply for capitals, AD, and ages over 60. This assumption may be too strong. For example, in the less developed states, we may be overestimating the level of under-registration of deaths, since data quality should be higher in their capital cities. Also, we know little about the variation of under-registration of deaths by age, and nothing guarantees that correction factors of reported deaths at adult ages apply to older ages. Nevertheless, given our ignorance about

Table 3

Estimates of specific mortality rates (SMR per 100,000 inhabitants) from Alzheimer's disease for 2009-2013 for median education (4-7 years), by age and in women, based on the results of the negative binomial Bayesian regression model with prior distributions of probability, via meta-analysis.

Region/Capital/ Age (years)	2009		2010		2011		2012		2013	
	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI
North										
Porto Velho										
65-69	5.5	1.7; 11.7	3.1	0.6; 7.8	4.7	1.8; 9.6	6.0	2.4; 11.3	909	4.2; 20.1
85 or older	94.7	26.5; 203.1	52.9	10.7; 139.2	80.7	27.8; 161.0	103.3	37.5; 196.0	169.2	64.3; 344.4
Manaus										
65-69	11.2	6.5; 17.5	7.4	4.1; 11.4	11.6	6.8; 17.4	14.9	9.2; 22.4	14.2	8.6; 21.6
85 or older	410.2	228.0; 660.9	270.7	152.2; 431.8	423.8	521.9; 656.8	540.8	326.7; 841.1	519.1	308.7; 816.4
Rio Branco										
65-69	10.6	4.3; 18.7	14.2	7.2; 23.0	7.5	2.8; 13.6	13.1	606; 21.1	11.4	5.7; 19.6
85 or older	226.8	96.8; 407.7	303.1	138.7; 490.1	159.8	61.3; 297.6	208.5	138.1; 461.3	247.4	111.7; 411.5
Northeast										
Salvador										
65-69	27.3	19.4; 36.7	34.3	25.1; 46.5	34.3	24.6; 45.2	32.4	23.2; 43.0	27.5	19.8; 36.3
85 or older	1.141.3	796.0; 1,546.9	1,442.6	1,027.2; 1,955.2	1,431.3	1,057.1; 1,933.4	1,348.7	969.4; 1,823.9	1,157.1	802.8; 1,516.8
Recife										
65-69	14.3	9.5; 19.0	20.5	14.4; 26.9	17.1	11.8; 22.4	22.6	16.0; 29.4	21.1	14.8; 27.7
85 or older	454.2	309.6; 611.3	652.6	467.6; 885.6	546.3	379.6; 724.1	720.9	503.1; 954.4	670.3	473.3; 900.5
São Luís										
65-69	27.8	14.1; 47.0	22.4	11.5; 39.0	22.6	12.1; 38.4	37.5	20.0; 66.1	31.6	16.7; 52.6
85 or older	925.4	438.8; 1,574.1	741.3	361.7; 1,321.5	759.3	350.8; 1,284.5	1,258.0	602.5; 2,234.7	1,045.4	541.7; 1,807.9
Natal										
65-69	29.8	18.8; 44.1	30.4	19.8; 46.6	28.8	18.6; 42.9	34.3	20.9; 49.9	34.8	22.8; 51.5
85 or older	1.234.7	781.1; 1,862.9	1,276.5	771.4; 1,902.0	1,209.2	730.6; 1,760.9	1,432.2	877.3; 2,118.5	1,450.4	877.2; 2,099.4
Central										
Cuiabá										
65-69	13.2	6.4; 21.9	32.3	15.4; 54.4	26.5	14.8; 45.6	32.6	17.5; 54.7	25.0	13.4; 41.9
85 or older	357.7	170.4; 619.8	882.9	433.5; 1,556.3	722.2	343.7; 1,230.6	889.7	489.0; 1,5947.4	689.3	378.2; 1,185.9
Goiânia										
65-69	19.8	13.6; 27.5	29.7	21.0; 42.2	30.2	20.0; 40.9	33.4	23.5; 47.0	28.8	20.1; 40.2
85 or older	785.5	539.3; 1,102.2	1,181.3	788.5; 1,647.3	1,195.5	819.0; 1,673.9	1,236.2	881.0; 1,869.4	1,149.3	790.8; 1,594.6
Campo Grande										
65-69	18.7	12.0; 26.2	26.0	17.8; 36.1	23.5	15.4; 33.0	27.7	17.9; 38.6	25.1	16.4; 35.1
85 or older	453.3	291.5; 633.6	628.9	423.2; 887.5	566.9	382.7; 821.5	671.2	458.1; 965.8	612.3	412.5; 867.5
Brasília (Federal District)										
65-69	16.4	10.7; 23.4	21.8	14.3; 31.2	17.3	11.3; 24.3	22.5	15.6; 31.8	29.5	20.4; 41.1
85 or older	584.5	361.3; 853.9	784.7	507.4; 1,133.6	617.4	418.0; 901.0	812.5	532.4; 1,161.4	1,067.9	704.1; 1,532.6

(continues)

Table 3 (continued)

Region/Capital/ Age (years)	2009		2010		2011		2012		2013	
	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI
Southeast										
Belo Horizonte										
65-69	35.9	25.2; 50.0	36.9	25.4; 51.0	42.8	29.9; 58.0	41.9	28.5; 56.6	38.3	27.7; 53.3
85 or older	1,837.2	1,227.3; 2,554.3	1,877.4	1,233.8; 2,554.9	2,180.2	1,441.6; 2,906.3	2,148.7	1,508.4; 2,994.4	1,953.7	3,384.9; 2,664.7
Vitória										
65-69	41.3	24.1; 64.1	45.4	24.9; 70.4	53.8	31.9; 80.1	50.6	29.6; 76.8	63.7	39.1; 95.4
85 or older	1,301.7	721.4; 2,011.1	1,438.9	816.4; 2.270.4	1,709.7	944.1; 2,588.9	1,602.0	902.7; 2,487.6	2,007.8	1,207.6; 3,114.9
São Paulo										
65-69	27.4	22.1; 33.6	28.0	22.8; 34.5	30.9	25.2; 38.1	30.0	24.5; 36.8	30.0	24.2; 36.8
85 or older	1,745.4	1,397.9; 2,114.9	1,782.2	1,462.6; 2,117.9	1,965.0	1,587.7; 2,360.9	1,912.6	1,533.9; 2,293.9	1,905.2	1,564.2; 2,.324.2
Rio de Janeiro										
65-69	30.3	24.5; 37.2	32.1	26.0; 39.6	31.4	25.6; 38.4	31.1	25.4; 38.2	32.7	26.3; 40.1
85 or older	1,490.1	1,201.4; 1,801.3	1,587.2	1,266.0; 1,907.1	1,544.7	1,205.5; 1,857.6	1,534.7	1,225.4; 1,859.7	1,607.1	1,323.0; 1,966.7
South										
Curitiba										
65-69	33.0	22.2; 45.4	38.6	27.2; 56.2	45.0	30.9; 63.0	34.5	23.0; 47.6	38.8	26.4; 54.1
85 or older	1,674.3	1,138.8; 2,348.3	1,964.7	1,256.1; 2,727.2	2,274.1	1,504.5; 3,149.3	1,746.2	1,175.1; 2,419.6	1,966.2	1,320.3; 2,716.4
Florianópolis										
65-69	29.7	16.2; 49.3	31.7	17.4; 51.3	43.1	24.2; 70.4	47.9	25.0; 76.1	43.4	23.0; 71.3
85 or older	916.7	452.0; 1,514.2	972.5	50.31; 1,583.3	1,325.0	697.8; 2,170.1	1.469.9	802.4; 2,381.1	1,328.4	712.7; 2,255.5
Porto Alegre										
65-69	39.4	28.2; 52.7	52.8	37.8; 70.1	44.5	32.0; 59.3	45.1	32.4; 60.6	46.8	33.6; 61.8
85 or older	1,242.5	883.9; 1,694.2	1,665.4	1,197.1; 2,241.3	1,402.7	1,031.2; 1,899.3	1,427.8	1,008.6; 1,903.4	1,477.0	1,047.2; 1,944.5
All										
State capitals										
65-69	42.7	35.7; 51.0	48.3	40.2; 57.8	51.2	43.4; 60.9	54.6	45.4; 64.3	57.0	48.1; 67.5
85 or older	1,159.3	974.7; 1,379.4	1,312.4	1,095.3; 1.534.9	1,388.4	1,177.4; 1,630.4	1,479.1	1,260.8; 1,748.3	1.552.9	1,308.0; 1,813.5

95%CI: 95% confidence interval.

Note: the proportion of Alzheimer's disease out of all demetias was estimated via meta-analysis.

Source: estimates based on microdata from Brazilian Mortality Information System (SIM) and 2010 *Brazilian Population Census*.

the actual size of the underreporting of deaths from dementia [49], we hope that a correction factor of 10% (on average), such as the one we used, provides at least some correction for the potential under-registration of deaths for AD. Also, correction factors at the state level allow us, at the minimum, to incorporate regional variations in data quality.

Knowing about the limitations of traditional methods for correcting for underreporting of deaths, we also perform additional adjustments to the observed rates. We used a negative binomial Bayesian regression model, based on the hypothesis that there is a much higher percentage of underreporting of mortality from dementia than other causes; a common phenomenon in many countries [18,42] Despite the evolution in medical technologies and health systems [50], this percentage may remain around 50%. In the specific case of Brazil, Nitrini et al. [22] found that only 12.5% of the death certificates in the mortality database (SIM) mentioned AD or dementia among individuals with dementia. This figure gives an idea of how low the coverage can get. Therefore, we believe that the corrections we made to the original data sources, based on a priori information from a meta-analysis, were necessary so that the estimates become consistent with the probable mortality levels from this cause of death.

Except for significant interactions between age and sex, which indicated a higher risk of death among men in the younger age groups [27], we found no significant overall sex differences for mortality from dementia. Without the proposed adjustments, the differences by sex would exist and would go in the opposite direction compared to reported AD incidence rates by sex. Teixeira et al. [51] found

Table 4

Estimates of specific mortality rates (SMR per 100,000 inhabitants) from Alzheimer's disease for 2009-2013 for median education (4-7 years), by age and in men, based on the results of the Bayesian negative binomial regression model with prior distributions of probability, via meta-analysis.

Region/ Capital/Age (years)	2009		2010		2011		2012		2013	
	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI
North										
Porto Velho										
65-69	5.3	1.7; 11.5	3.0	0.6; 7.7	4.5	1.6; 9.2	5.8	2.0; 10.8	9.6	4.4; 20.1
85 or older	91.6	28.0; 198.1	50.8	8.4; 133.2	78.3	25.4; 154.2	100.5	34.4; 190.1	165.2	64.8; 347.5
Manaus										
65-69	10.6	6.1; 16.4	7.0	4.0; 10.8	11.0	6.5; 16.6	14.0	8.4; 20.9	13.4	8.2; 20.5
85 or older	386.6	212.4; 627.6	255.2	135.8; 400.1	400.5	243.9; 635.7	51.7	288.8; 783.7	487.5	290.2; 779.6
Rio Branco										
65-69	10.0	4.2; 18.5	13.5	6.6; 21.7	7.1	2.9; 13.1	12.4	6.2; 20.3	10.9	5.3; 19.0
85 or older	21.5.0	92.1; 389.0	288.3	136.4; 468.6	152.4	55.6; 277.5	266.9	143.3; 449.9	236.0	108.8; 398.6
Northeast										
Salvador										
65-69	24.9	17.0; 33.0	31.3	21.7; 41.8	31.1	22.2; 41.0	29.5	21.2; 39.2	25.1	17.9; 33.5
85 or older	1,042.9	697.2; 1,420.4	1,316.1	918.1; 1,766.0	1,311.3	944.3; 1,765.0	1,235.6	845.4; 1,643.0	1,051.5	727.3; 1,390.2
Recife										
65-69	14.5	9.8; 19.6	20.8	14.9; 28.2	17.3	12.3; 23.2	22.9	16.8; 30.9	21.4	15.4; 28.7
85 or older	461.0	329.7; 64.8	662.7	476.7; 911.5	550.5	393.8; 751.6	728.4	542.4; 999.4	682.1	475.0; 907.3
São Luís										
65-69	24.8	12.5; 42.4	20.0	10.1; 34.5	20.3	10.2; 34.4	33.5	18.1; 58.3	28.2	15.6; 47.4
85 or older	822.4	391.7; 1,434.4	662.2	342.1; 1,223.7	680.2	338.7; 1,173.3	1.116.7	533.8; 1,989.5	936.5	454.7; 1,599.0
Natal										
65-69	26.6	16.6; 39.2	27.2	17.5; 41.7	25.8	16.3; 38.0	30.5	20.0; 45.9	31.0	19.2; 44.9
85 or older	1,104.2	678.4; 1,674.7	1,140.2	681.8; 1,717.9	1,084.3	652.4; 1,597.4	1,276.7	798.7; 1,917.8	1,298.7	778.6; 1,940.1
Central										
Cuiabá										
65-69	12.0	6.2; 20.9	29.4	15.5; 51.0	24.2	12.7; 41.2	29.6	15.3; 49.7	23.0	11.6; 37.8
85 or older	327.5	155.2; 574.0	800.4	380.4; 1,444.0	659.5	334.5; 1,156.9	812.4	385.9; 1,406.0	630.6	312.5; 1,047.7
Goiânia										
65-69	18.5	12.5; 25.5	27.6	19.0; 38.6	28.1	19.3; 38.6	32.1	21.0; 43.3	26.9	18.0; 37.2
85 or older	733.2	494.1; 1,036.4	1,110.8	722.4; 1,534.6	1,117.0	747.3; 1,541.6	1,233.7	817.9; 1,769.8	1,068.0	726.9; 1,497.6
Campo Grande										
65-69	17.8	11.6; 25.3	24.9	16.2; 34.5	22.5	14.6; 31.8	26.5	17.4; 38.0	24.0	16.2; 34.3
85 or older	432.5	280.6; 616.2	604.8	403.6; 864.7	542.8	351.1; 780.3	642.1	422.6; 931.9	585.4	394.7; 851.4
Brasília (Federal District)										
65-69	17.1	11.3; 25.1	22.8	15.1; 32.4	18.1	11.9; 25.5	23.6	15.5; 32.6	31.0	21.2; 43.5
85 or older	614.4	380.9; 898.8	824.1	521.2; 1.189.4	648.3	419.2; 922.1	850.2	254.7; 1,210.0	1,108.0	754.5; 1,627.1

(continues)

Table 4 (continued)

Region/ Capital/Age (years)	2009		2010		2011		2012		2013	
	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI
Southeast										
Belo Horizonte										
65-69	33.4	23.5; 46.4	34.2	24.1; 47.7	39.7	27.8; 45.1	39.0	28.0; 53.6	35.6	25.3; 48.2
85 or older	1,712.5	1,145.9; 2,377.7	1,753.2	1,196.3; 2,442.5	2,208.9	1,420.6; 2,874.6	1,990.6	1,396.5; 2,769.4	1,815.6	1,251.5; 2,495.9
Vitória										
65-69	38.7	23.0; 60.7	42.8	24.0; 66.3	50.7	29.5; 75.6	47.7	27.6; 72.5	60.0	35.8; 88.8
85 or older	1.236.5	701.9; 1,936.4	1,362.0	725.6; 2,120.6	1,599.3	920.0; 2,510.6	1,508.9	879.0; 2,394.0	1,894.8	1,074.0; 2,910.0
São Paulo										
65-69	30.0	24.1; 36.5	30.7	24.9; 37.6	33.7	27.5; 41.4	32.9	26.9; 39.9	32.8	26.3; 39.8
85 or older	1,917.4	1,521.5; 2,322.3	1,952.2	1,589.6; 2,389.8	2,153.9	1,748.2; 2,610.4	2,091.6	1,693.6; 2,532.2	2,084.3	1,707.3; 2,544.0
Rio de Janeiro										
65-69	29.9	24.3; 36.9	31.9	25.2; 39.1	31.0	34.7; 37.6	30.7	25.2; 37.6	32.2	26.0; 39.5
85 or older	1,470.9	1,152.6; 1,780.2	1,567.4	1,255.2; 1,909.8	1,525.7	1,225.2; 1,843.3	1,512.3	1,228.8; 1,837.0	1,592.0	1,283.2; 1,936.9
South										
Curitiba										
65-69	29.6	19.9; 40.5	34.6	23.6; 48.9	40.5	27.5; 56.0	30.8	20.8; 43.0	34.8	23.5; 48.4
85 or older	1,491.7	1,012.5; 2,123.8	1,756.6	1,152.0; 2,451.2	2,036.3	1,382.7; 2,858.6	1,553.5	1,063.8; 2,223.5	1,765.9	1,140.4; 2,435.1
Florianópolis										
65-69	24.9	12.8; 41.7	26.7	14.0; 43.7	36.4	19.4; 58.9	40.5	21.5; 67.1	36.7	19.3; 60.6
85 or older	767.1	411.6; 1,336.3	817.2	399.4; 1,349.6	1,116.8	584.1; 1,863.2	1,249.9	646.5; 2,049.4	1,121.1	557.9; 1,898.0
Porto Alegre										
65-69	46.5	32.9; 61.8	62.4	45.0; 82.5	52.3	37.7; 69.5	53.3	38.0; 70.4	55.5	39.2; 72.8
85 or older	1,466.3	1,023.1; 1,986.2	1,970.5	1,368.7; 2,629.6	1,651.0	1,173.7; 2,225.5	1,687.0	1,175.3; 2,263.3	1,750.3	1,191.4; 2,299.1
All										
State capitals										
65-69	19.0	15.5; 22.4	21.5	18.0; 25.5	22.8	19.4; 27.1	24.3	20.4; 28.7	25.4	21.5; 30.1
85 or older	462.8	380.4; 546.8	523.7	437.3; 612.2	553.8	467.3; 654.2	590.4	493.1; 692.1	619.0	522.3; 724.8

95%CI: 95% confidence interval.

Note: the proportion of Alzheimer's disease out of all demetias was estimated via meta-analysis.

Source: estimates based on microdata from Brazilian Mortality Information System (SIM) and 2010 *Brazilian Population Census*.

Alzheimer-specific mortality rates of 88.5 per 100,000 among men and 112 per 100,000 among women in 2009. These estimates were similar to our crude rates, calculated before the proposed adjustments. There is an extensive discussion in Mazure & Swendsen [52] about this subject, but it is important to note that other studies [34,37,38] found no statistically significant differences in AD incidence by sex, which is consistent with our results [53].

The regional differences in SMR are another critical result. Curiously, mortality from AD is higher in the Southeast and South regions of Brazil. One explanation is that the reporting of AD cases may be of higher quality in the more developed regions. Although we adjusted for the underreporting of deaths by state, mortality levels (including overall mortality) may still be underestimated at the higher ages, particularly in the less developed regions, for other reasons like age misreporting in the death records. On the other hand, the fact that the less developed regions are at a less advanced stage in the epidemiological transition may imply in a higher incidence of other causes of mortality, thereby reducing the relative importance of dementia than in the more developed regions (Southeast and South).

The risk of dying from dementia and AD increases with age [24,46]. At older ages, the highest mortality rates from Alzheimer's disease were among adults with less schooling (0-3 years). In this case,

the rates were around 1,710.5 deaths per 100,000 inhabitants, almost twice as large as among adults in the highest education group. Education works as a possible protective factor against all types of dementia. "Cognitive reserve" is relevant since we found that individuals with all types of dementia in lowest educational level (0-3 years) contributed with 6% of overall adult mortality, and 4.4% in the case of AD. The estimates by education were a significant challenge in our study. Missing data by educational level could have impacted the final results, which justified the data imputation. Nevertheless, the imputation was also not trivial, given the volume of missing data and the uncertainty about the actual distribution of cases by educational level. Also, it was challenging to measure the impact of the inconsistency in the information reported by education in the mortality and population records, since these two data sources were collected separately [54]. Even so, there was evidence of greater consistency in the model with the addition of imputed data [27].

In relation to the risk of dying from dementia or AD, our results indicated a clear qualitative difference between 3 years of schooling or less and 4 years or more, which has also been observed in other contexts [22,44,45,55] in Brazil. Highly educated individuals tend to have better opportunities and probably more comfortable retirement [56]. We thus believe that education appears as a proxy variable explaining socioeconomic inequalities, more than the relationship of education and mortality from AD at older ages per se.

The increase in life expectancy, new technologies, and better diagnostics can lead to the impression that AD is increasing. In fact, the higher incidence may be due to our better capacity for diagnosis as the elderly population grows. Therefore, cases not previously detected and that were classified as other types of diseases may now be identified more accurately. In addition, environmental factors can now be included in the analysis [57].

Contributors

J. J. Sandoval participated in the conception and design of the study, statistical analysis, interpretation of data and writing of the article, taking responsibility for all aspects of the work. C. M. Turra participated in the relevant critical review of the intellectual content and the final approval of the article to be published. R. H. Loschi collaborated in the statistical analysis and final interpretation of the results.

Additional informations

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Resumen

Este artículo proporciona estimaciones de las tasas de mortalidad por la demencia por la enfermedad de Alzheimer (DA) en población adulta mayor. Para ello, se usaron datos del Censo Demográfico *de 2010 del Instituto Brasileño de Geografía y Estadística (IBGE) y microdatos de mortalidad de las 27 capitales de los estados brasileños, registradas en el Sistema de Informaciones sobre Mortalidad (SIM) del Ministerio de Salud de Brasil, en población con 65 años o más por lugar de residencia, entre los años 2009 y 2013. Se obtuvieron correcciones de los subregistros de mortalidad y ajustes finales de las tasas específicas de mortalidad, a partir de métodos bayesianos, con distribuciones de probabilidad a* priori*, construidas en base a información obtenida desde metaanálisis. Se destaca que las tasas por demencia y DA en Brasil fueron superiores a las obtenidas en países desarrollados. Las tasas de mortalidad por Alzheimer en 2013 fueron de 140,03 (IC95%: 117,05; 166,4) y 127,07 (IC95%: 103,74; 149,62) por 100.000 habitantes, respectivamente, en hombres y mujeres. La contribución de la DA a la mortalidad adulta mayor en el Brasil fue 4,4% (IC95%: 3,25; 5,72), en el grupo de personas de 0 a 3 años de estudio, independiente de la edad y sexo. Nuestras contribuciones fueron dirigidas a aumentar el conocimiento en estimaciones corregidas de las tasas de mortalidad por Alzheimer con base en estadísticas vitales, proporcionando estimaciones más precisas y pertinentes, fundamentadas en el método científico.*

Demencia; Enfermedad de Alzheimer; Mortalidad; Análisis de Bayes; Metanálisis

Resumo

Este artigo oferece estimativas das taxas de mortalidade devidas à demência pela doença de Alzheimer (DA) na população idosa brasileira. Para isso, foram usados dados do Censo de Demográfico *de 2010 do Instituto Brasileiro de Geografia e Estatística (IBGE) e microdados de mortalidade das 27 capitais dos estados brasileiros, registradas no Sistema de Informações sobre Mortalidade (SIM) do Ministério da Saúde, em população com 65 anos ou mais por local de residência, entre os anos de 2009 e 2013. Foram obtidas correções dos sub-registros de mortalidade e ajustes finais das taxas específicas de mortalidade, a partir de métodos bayesianos, com distribuições de probabilidade a priori, construídas em base a informações obtidas via meta-análises. Foi destacado que as taxas por demência e DA no Brasil foram superiores às obtidas em países desenvolvidos. As taxas de mortalidade por Alzheimer em 2013 foram de 140,03 (IC95%: 117,05; 166,4) e 127,07 (IC95%: 103,74; 149,62) por 100 mil habitantes, respectivamente, em homens e mulheres. A contribuição da DA para a mortalidade em idosos no Brasil foi 4,4% (IC95%: 3,25; 5,72), em um grupo de pessoas com 0 a 3 anos de estudo, independentemente da idade ou sexo. Nossas contribuições foram dirigidas a aumentar o conhecimento em estimativas corrigidas das taxas de mortalidade por Alzheimer com base em estatísticas vitais, proporcionando estimativas mais precisas e pertinentes, fundamentadas no método científico.*

Demência; Doença de Alzheimer; Mortalidade; Análise de Bayes; Metanálise

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