Hospitalization of the elderly for alzheimer's disease in Brazil, and associated costs: an echological study

Internação hospitalar de idosos por doença de alzheimer no Brasil, ecusto associado: estudo ecológico

Tainá Medeiros Duarte da Silva[1*], Maria Eduarda Pereira de Lambert Oliveira[2], Fabiana Oenning da Gama[3], Rodrigo da Rosa Iop[4], Franciele Cascaes da Silva[5]

[1]Medical Student. University of Southern Santa Catarina, UNISUL, Palhoça/ SC, Brazil, [2]Medical Student. University of Southern Santa Catarina, UNISUL, Palhoça/ SC, Brazil, [3]Master in Psychopedagogy and Expert in Intensive Care. Professor in the Medical Course at University of Southern Santa Catarina, UNISUL, Palhoça/ SC, Brazil, [4]PhD in Human Movement Science, professor in the Physical Therapy Course. University of Southern Santa Catarina, UNISUL, Florianópolis/ SC, Brazil, [5]PhD in Human Movement Science, professor in the Medical Course. University of Southern Santa Catarina, UNISUL, Palhoça/ SC, Brazil

*Corresponding author:: Tainá Medeiros Duarte da Silva – E-mail: taina_hpwg@hotmail.com

ABSTRACT

The high prevalence of dementias, where the population enjoys greater longevity, makes the need to conduct research related to Alzheimer's Disease important, thus we aimed to analyze the temporal trend of hospital admissions of the elderly for Alzheimer's disease in Brazil, and associated cost, between 2008-2020. An ecological study of analysis of time series, using records from the Hospital Information System. It was identified that the overall rate ($ß = 0.203$; $p = 0.009$), in both sexes ($p \leq 0.05$), in the 80 and older age group ($ß = 1.081$; $p = 0.002$) and in all regions of Brazil ($p \leq 0.05$) showed an increasing trend. The total cost of hospitalization was R$ 27,617,699.74 and the average cost was R$ 2,124,438.44. It is concluded that the time trend of hospitalization of the elderly for Alzheimer's disease was increasing in Brazil between 2008-2020, and the associated costs are considerable.

Keywords: Alzheimer's Disease. Hospitalization. Elderly.

RESUMO

A alta prevalência de demências, onde a população goza de uma maior longevidade, torna-se importante a necessidade de realizar pesquisas relacionadas à Doença de Alzheimer, assim objetivou-se analisar a tendência temporal de internação hospitalar de idosos por Doença de Alzheimer no Brasil, e custo associado, entre 2008-2020. Estudo ecológico de séries temporais, utilizando registros do Sistema de Informação Hospitalar. Identificou-se que a taxa geral ($ß = 0,203$; $p = 0,009$), em ambos os sexos ($p \leq 0,05$), na faixa etária de 80 anos ou mais ($ß = 1.081$; $p = 0,002$) e em todas as regiões do Brasil ($p \leq 0,05$) apresentou tendência crescente. O custo total de internação foi de R$ 27.617.699,74 e o custo médio de R$ 2.124.438,44. Conclui-se que a tendência temporal de internação hospitalar de idosos por Doença de Alzheimer está crescente no Brasil entre 2008-2020, e os custos associados são consideráveis..

Palavras-chave: Doença de Alzheimer. Hospitalização. Idoso.

INTRODUCTION

Population ageing occurs due to the balance between the birth and mortality rate, together with the increase of life expectancy from birth.[1] According to the Brazilian National Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* - IBGE), in 2019, the elderly aged 65 or older represented 9.52% of population. With the projections, it is foreseeable that in 2060 they will represent 25.49% of population. In the same way, it is possible to note that the birth rate will be controlled, going from 13.79% in 2021 to 9.29% in 2060, and that there will be an increase in the mortality rate, which will go from 6.61 to 12.51 in the same years. Furthermore, life expectancy from birth was 76.6 years in 2019, and it shall increase to 81.4 in 2060.[2]

As life expectancy from birth increases and population ages, Noncommunicable diseases (NCDs) become more relevant and prevalent in the medical scope.[1,3] Among many NCDs, dementias are highlighted.[1] According to Alzheimer's Disease International (ADI), the amount of people living with dementia in 2020 was 50 million, which shall increase to 152 million in 2050.[4] Representing around 70% of cases of dementia, Alzheimer's Disease (AD) is prevalent.[5]

AD is a chronic neurodegenerative disease that affects the central nervous system, and one of its main and well-known symptoms is amnesia.[6–8] It has been showing higher levels as Brazil's demography rapidly transitions, along with other various ageing diseases, which has become a relevant topic for public health. Its prevalence is approximately of 25 million cases around the world.[7] In Brazil, there are 1.2 million cases of dementia due to AD.[9] It mostly affects the elderly, and the chances of developing it are almost doubled at every 10 years after 65 years old.[7,9]

The disease can be caused by the association of genetical, behavioral, and environmental factors.[1,7] Symptomatology arises insidiously [7,10,11] and, as the disease progresses, other signs and symptoms appear.[7] In its most severe form, patients present deterioration of multiple cognitive domains and, as a consequence, basic activities are compromised. This can lead to death around ten years after the symptoms begin.[6,7,10,13]

Efficient methods and medication for the treatment have not yet been discovered in order to slow the progression of the disease or allow its cure. Thus, AD's treatment is based on symptomatic medications.[11,13] Nonetheless, these patients need to be cared of by a multiprofessional, especially as the disease progress.[3,5]

In this scenario and due to the high prevalence of dementias where the population enjoys greater longevity, the need to conduct research related to the Alzheimer's Disease becomes important.[14] This disease directly affects the quality of patient's life as they lose their functional capacity and autonomy, which causes morbimortality to increase and results in hospitalization with the need of a multiprofessional care. It all significantly impacts the costs with healthcare.[1,12]

After surveying the specialized literature, one may conclude that the studies whose topic is hospital admission for AD in Brazil are principiant, since most of them discuss the epidemiology, pathogeny, diagnostics, therapy, and the socioeconomical impact of the disease.[1,5–7,10–12,14] In this sense, the present study aims to analyze the temporal trend of hospitalization of the elderly for Alzheimer's Disease in Brazil, and associated cost, between 2008-2020, which can work as subsidies to the implementation of public and preventive policies by means of early diagnostics and preventive care, allowing for the decrease of the socioeconomical impact of the disease.

METHODOLOGY

STUDY TYPE

An ecological study of analysis of time series, with secondary data, using records from the Hospital Information System/Unified Health System (*Sistema de Informações Hospitalares - SIH / Sistema Único de Saúde - SUS*), made available by the Department of Informatics of the Ministry of Health (*Departamento de Informática do Ministério da Saúde - DATASUS*), an online platform with public access that makes available information on TABNET at http://www.datasus.gov.br, with a copy in the Comma Separated Value (CSV) format.

DATA COLLECTION

The study included the hospitalization of the elderly from both sexes for Alzheimer's Disease, aged 60 years old on, from 2008 to 2020, full year information available for access, and per region of the country, totaling 14,419 cases.

Data collection from SIH/ SUS was carried out by means of the software TABWIN, available at DATASUS, and tabulation by means of Microsoft Excel® (2010). General hospitalization rates, per sex, age group, and region of the country were calculated by 100,000 (one-hundred thousand) inhabitants, having as denominator the general total and population sex. Population data were based upon the results of the 2010 Demographic Census, made available by the Brazilian National Institute of Geography and Statistics (IBGE). The Census' population count was used as denominator for the series of the 2008 to 2010 years. Additionally, population estimates were used for the period from 2011 to 2020.

Hospitalization numbers and coefficients for each year of study were stratified according to the following variables: a) sex (male; female);

b) age group (60-69 years old; 70-79 years old; 80 years old or older); c) regions of the country (North; Northeast; Southeast; South; Mid-West); d) sex and age group.

STATISTICAL ANALYSIS

Initially, hospitalization counting for each year of study were entered in Microsoft Excel®. Then, the general and stratified hospitalization rates according to sex, age group, region of the country, and age group per sex were calculated per 100,000 inhabitants as per the following formula: Specific rate = Hospitalization counting of the elderly for AD according to sex, age, region of the country x 100,000 / by the reference Population for the period according to sex, age and region of the country.

The associated cost of hospitalization was obtained from SIH/SUS and the total cost of hospitalization per year along with the average cost of hospitalization, both in reais (R$), were presented.

For the trend analysis of time series, the simple linear regression model was used by means of the software Statistical Package for the Social Sciences 2.0 (SPSS, IBM®, Chicago, IL, EUA). In this model, the hospitalization rates were considered dependent variables, and the calendar years of the study were considered independent variable. Thus, the estimate model was obtained from the formula: $Y = b0 + b1X$ where Y = standardized coefficient, $b0$ = average coefficient for the period, $b1$ = average annual gain and X = year. The significance level considered was 5%.

Furthermore, the annual percentage variance calculus (VAP) was carried out by subtracting the rate amount of the last year and the rate amount of the first year and dividing this difference by the amount of the rate of the first year.

ETHICAL ASPECTS

This study was exclusively conducted using secondary added data, of public access and in conformance with the National Health Council (CNS) under Resolution number 466 from December 12th, 2012, and with the guidelines and standards of Resolution 510/2016 of the National Health Council, Article 1, Sole Paragraph, Subparagraph II, III and V. Hence, this study was dismissed from the review by the Research Ethics Committee

RESULTS

A total of 14,419 cases of hospitalization of the elderly for Alzheimer's Disease in Brazil were analyzed during 2008-2020. Figure 1 shows that the general hospitalization rate (ß= 0.203; p= 0.009) and in both sexes (Male ß= 3.350, p= 0,015; Female ß= 0.255; p= 0.007) presented an increasing trend. Women presented higher average rate (5.44) and higher annual percentage variance (0.83%)
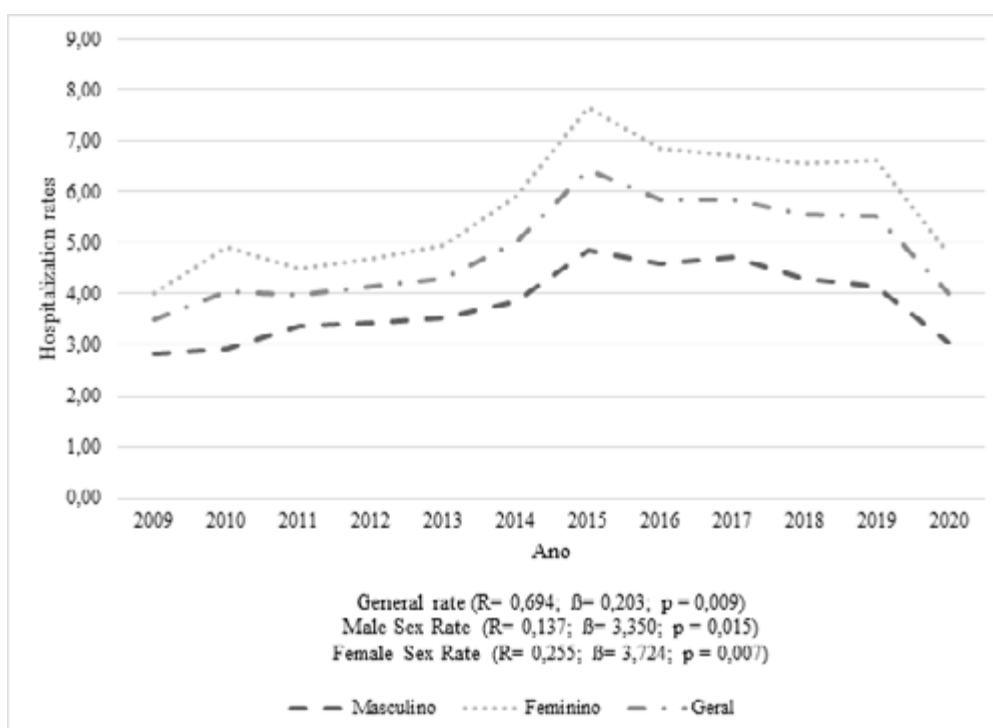

Figure 1. General rate of hospitalization of the elderly for Alzheimer's Disease in Brazil during 2008-2020 and according to sex.

The trend analysis of the hospitalization rate of the elderly for Alzheimer's Disease according to age group showed an increasing trend in the 80 or older age group (ß= 1,081; p= 0,002), with annual percentage variance of 1.21%. All Brazilian regions presented an increasing trend, Northeast, Mid-West, and South being the ones that presented the highest annual percentage rate analysis, with 3.57%, 3.45%, and 2.06% respectively (Table 1)

Table 1. Temporal trend of hospitalization of the elderly for Alzheimer's Disease in Brazil between 2008-2020 according to age group and regions.

	Average Rate	VAP	R (*)	R2 (†)	B (‡)	Amount p	Trend
Age							
60 - 69 years old	0.831	0.01	0.504	0.254	0.23	0.079	-
70 - 79 years old	5.047	0.21	0.477	0.227	0.126	0.100	-
≥ 80 years old	19.480	1.21	0.763	0.582	1.081	0.002	↑
Regions							
South	0.943	2.06	0.903	0.815	0.056	0.000	↑
Southeast	0.750	0.84	0.725	0.526	0.049	0.005	↑
Mid-West	0.367	3.45	0.905	0.818	0.45	0.000	↑
North	0.179	0.90	0.728	0.531	0.008	0.005	↑
Northeast	0.183	3.57	0.952	0.906	0.21	0.000	↑

VAP, annual percentage variance (VAP); R (*) - correlation coefficient; R2(†) - coefficient of determination; ß (‡) - linear regression coefficient.↑ Increasing; ↓ Decreasing; - Constant

The trend analysis of the hospitalization rate of the elderly for Alzheimer's Disease between 2008-2020 according to sex and age group showed a decreasing trend for men in the 70-79 age group (ß= -0,109; p= 0,021) with annual percentage variance of 1,56%. For women, the decreasing trend was observed in the 60-69 (ß= -0,042; p= 0,050) and 70-79 age group (ß= -0,133; p= 0,013). However, the highest annual percentage variance was among the elderly aged 80 years old or older (1.44%) (Table 2)

Table 2. Temporal trend of hospitalization of the elderly for Alzheimer's Disease in Brazil between 2008-2020 according to age group and regions.

	Average Rate	VAP	R (*)	R² (†)	ß (‡)	Amount p	Trend
Male							
60 to 69 years old	2.29	0.08	0.071	0.005	-0.010	0.817	-
70 to 79 years old	4.49	1.56	0.630	0.397	-0.109	0.021	↓
80 years old or older	5.92	2.49	0.356	0.127	-0.115	0.233	-
Female							
60 to 69 years old	1.27	-0.30	0.553	0.305	-0.042	0.050	↓
70 to 79 years old	2.94	0.40	0.666	0.443	-0.133	0.013	↓
80 years old or older	4.30	1.44	0.309	0.096	-0.095	0.304	-

VAP, annual percentage variance (VAP); R (*) - correlation coefficient; R²(†) - coefficient of determination; ß (‡) - linear regression coefficient.↑ Increasing; ↓ Decreasing; - Constant

The average hospitalization duration was 28.61 ± 8.92 days, resulting in a total cost, for this period, of R\$ 27,617,699.74, and in an average cost of hospitalization of R\$ 2,124,438.44 (Table 3)

Table 3. Hospitalization costs for Alzheimer's Disease in Brazil between 2008-2020.

Year of Attendance	Total Amount
2008	3,389,706.27
2009	1,385,657.44
2010	2,391,872.32
2011	1,365,450.69
2012	2,126,100.54
2013	2,270,911.00
2014	2,777,063.24
2015	2,300,742.73
2016	2,342,988.08
2017	2,081,511.30
2018	1,933,666.96
2019	2,101,040.43
2020	1,150,988.74
Total	**27,617,699.74**
Average annual amount	**2,124,438.44**

DISCUSSION

The present study presented a temporal trend of hospitalization of the elderly for Alzheimer's Disease in Brazil, and associated costs between 2008-2020. In this period of analysis, it was identified that the general rate, for both sexes, in the 80 or older age group and in the regions of the country, presented an increasing trend. Women presented higher average rate and higher annual percentage variance. For men, the decreasing trend was present among the elderly aged 70-79 years old, while for women, this decrescent trend was observed in the 60-69 and 70-79 age group. The total cost was R$ 27,617,699.74 and the average annual cost of hospitalization was R$ 2,124,438.44.

The increasing trend noted in the general rate highlights a clear association with the demographic transition of Brazilian population, correlating the increase in life expectancy with the increase of senile diseases, such as the Alzheimer's Disease, since it is expected that dementia increases worldwide as the population progressively ages.[12] From 2000 to 2007, a total of 19% of patients in North-American nursing homes who died for advanced dementia, had been hospitalized during their last 3 days of life or had been hospitalized multiple times during their last 90 days of life, or were cared of in multiple nursing homes after hospitalization in the last 90 days of their lives.[13]

Regarding the increasing trend according to sex, women were in evidence due to higher life expectancy, since they live 9 years more than men, which represent 55.5% of the elderly Brazilian population and 61% of the elderly above 80 years old. [1] Furthermore, women visit doctors more often as they are more concerned with life quality and general welfare.[15]

This outcome corroborates many studies whose results showed higher hospitalization rates for women when compared to men.[8,9,16] Among them are the cross-sectional epidemiologic descriptive study, that analyzed 9,081 hospitalizations that took place in Brazil from

2013 to 2017, 63.40% for women and 36.60% for men.[16] Another epidemiologic descriptive study also observed that 1,112 out of 1,716 hospitalizations registered in Brazil from July 2017 to July 2018 were for women and 604 for men.[8] Finally, the ecological study reported 12,150 hospitalizations between 2008 and 2018, 64.54% for women and 35.46% for men.[9]

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The 60-69 and 70-79 age group remained steady, while the ≥ 80 age group showed an increasing trend, which can be explained by the fact that population is living longer each year, linking longer life expectancy to the also increasing risk of developing Alzheimer's Disease.[8] The same result was found in a descriptive epidemiologic study, whose data were collected using records from the Hospital Information System (SIH) and from the Unified Health System (SUS) database, made available by SUS' informatics department (DATASUS), where the base population for the study came from in order to be used for all cases of Alzheimer's Disease for both sexes, above 50 years, diagnosed and recorded between July 2017 and July 2018.[8]

The sex and age group analysis showed a decreasing trend for men in the 70-79 age group. For women, the decreasing trend was present in the 60-69 and 70-79 age group. However, the highest annual percentage variance was among the elderly aged 80 years old or older. These outcomes corroborate the study conducted by Santos *et al.*[3], where it is demonstrated that for both sexes and age groups under study,

the hospitalization coefficient of the elderly for mental and behavioral disturbs, including dementia, in Brazil decreased during the 2008 and 2014 period.

An ecological study[9] that assessed morbidity and mortality of the Alzheimer's' Disease in hospitalized individuals in Brazil between 2008 and 2018 showed that men above 80 years old had the lowest average of hospitalization prevalence (23.1 days), and, among women, the highest average was 39.7 days for those aged 60-69. In the present study, the hospitalization average prevalence was 28.61 days.

All of the regions showed an increasing trend, which as more evident in the south, mid-west, and northeast. This can be explained due to the increasingly development of the country as a whole, as well as of the regions where once showed worse social development milestones. The demographic transition level 4 where the country currently is matches the data discovered. In the study conducted by Crisóstomo et al., the macroregions with a predominant increase were the southeast, with 1,001 reported cases, followed by the south, with 383, the northeast, with 177, the mid-west, with 115, and the north, with 40, between 2017 and 2018. The outcome is similar to Santos', Pinheiro's, and Ribeiro's study, considering that the southeast presented the highest rate of hospitalization among Brazilian regions, 7,168 (59%), followed by the south, with 2,994 (24.65%), the northeast with 1,066 (8.77), the mid-west, 579 (4.76) and the north, with the lowest rate: 343 reported cases, which represents 2.82% of hospitalizations. The study conducted by Silva et al. also shows the total hospitalizations trend related to the regions, 67.8% (n=6.157) being in the southeast, 18.5% (n=1,679) in the south, 7.7% (n=704) in the northeast, 3.8% (n=347) in the mid-west, and 2.1% (n=194) in the north.

An analysis of 38 epidemiologic studies from 1994 to 2000 was carried out to identify

the prevalence of dementia in different regions around the world: Europe, Asia, North America, South America, Oceania, and Africa using Medline and Lilacs databases. An increase of dementia prevalence according to the ageing of the population and an increase by 75% of dementia prevalence in women in the regions under study were highlighted. The prevalence of AD is also confirmed in all continents when compared to vascular dementia, South America being in evidence, with results twice or three times bigger.[17]

In respect to the costs of hospitalization for Alzheimer's Disease in Brazil, there is a similarity regarding the years of study. According to the World Health Organization (WHO), the global cost of individuals with dementia in the year of 2010 was around US$ 604 billion.[1] The total global cost for the society of a population of 34.4 million people with dementia was approximately US$ 422 million in the year of 2009 plus US$ 142 million with informal care. It is concluded, then, that the global cost with dementia increased 34% from 2005 to 2009.

In 1998, Meek at al.[1] found out that the Alzheimer's Disease was the third more expensive disease in the USA; Brookmeyer et al. [1] said that the costs with health care for patients with AD peaked U$ 36 billion a year in the US economy. In the United Kingdom, 17 billion euros a year are spent with dementia diseases, and this amount is estimated to increase through years. [1] In 2010, the cost with dementia in Spain was above 16 billion, representing 15% of total health expenses.[12] Dementia is classified as the second neurologic disease that demands more health costs, behind multiple sclerosis.[12] Health costs of patients with AD area 34% higher than those of a similar population without the disease, since it is related to paying more visits to emergency care, to more hospitalization, to more hospital prevalence, and to a greater need for home healthcare.[12]

It is known that the social cost with AD care increases according to the level of daily life activities' dependency, the deterioration of cognitive function, the presence of comorbidities, to neuropsychiatric disorders, extrapyramidal[12] symptoms, and according to the disease progress and severity, institutionalization acting as the main driving force. It is then concluded that chronic neurodegenerative diseases, such as dementias, represent a big problem for the public health and have a huge socioeconomic impact in the world.[5]

The present study shows limitations regarding the use of secondary data obtained from SIH/SUS and made available by DATASUS, such as lack of standards when collecting and recording the hospitalization data that took place under the SUS, which represents only a portion of the national reality. However, DATASUS is widely used to assess the costs of health care services, and governmental databases is a reliable and legitimate source, allowing for interventions and providing subsidies for decision making. Despite limitations, the results found could assist in the implementation of preventive actions aimed at the elderly and for early diagnostic, as well as treatment. Such measures could be carried out by means of a validated questionnaire for cognitive evaluation, for undergoing diagnostic and early staging image examination, and for acquisition of medications and other tools that slow the progression and evolution of the disease. It could contribute to reducing hospitalizations and to applying the costs with it in other health services, besides minimizing the socioeconomic impact of the disease.

CONCLUSION

It is concluded that the temporal trend of hospitalization of the elderly for Alzheimer's Disease has increased in Brazil between 2008-2020, showing higher rates for women in the 80 or older age group and in the Northeast, Mid-West, and Southeast regions of Brazil, totaling R$ 27,617,699.74 and R$ 2,124,438.44 as annual average.

EPIDEMIOLOGIC APLICATIONS

Becoming aware of the hospitalization rate of the elderly with Alzheimer's Disease is important to help formulate public politics that can reduce this rate, offer better assistance with the primary attention, and provide a healthy ageing.

REFERENCES

1. Dos Santos C de S, de Bessa TA, Xavier AJ. Factors associated with dementia in elderly. Ciênc e Saúde Colet. 2020;25(2):603–11. DOI 10.1590/1413-81232020252.02042018

2. IBGE. Instituto Brasileiro de Geografia e Estatística.Tábua completa de mortalidade para o Brasil – 2019: breve análise da evolução da mortalidade no Brasil. 2020; Available from: https://agenciadenoticias.ibge.gov.br/media/com_mediaibge/arquivos/65c3023462edaabf-0d7318c1a0f80ca4.pdf

3. Santos VC, Anjos KF Dos, Boery RNS de O, Moreira RM, Cruz DP, Boery EN. Internação e mortalidade hospitalar de idosos por transtornos mentais e comportamentais no Brasil, 2008-2014. Epidemiol. e Serv. Saúde Rev do Sist Unico Saude do Bras. 2017;26(1):39–49. DOI 10.5123/S1679-49742017000100005

4. Alzheimer's Disease International [Internet]. Dementia statistics. Available from: https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/

5. Gutierrez BAO, da Silva HS, Guimarães C, Campino AC. Impacto econômico da doença de Alzheimer no Brasil: é possível melhorar a assistência e reduzir custos? Ciênc e Saúde Colet. 2014;19(11):4479–86. DOI 10.1590/1413-812320141911.03562013

6. Beydoun MA, Gamaldo AA, Beydoun HA, Shaked D, Zonderman AB, Eid SM. Trends, Predictors, and Outcomes of Healthcare Resources Used in Patients Hospitalized with Alzheimer's Disease with at Least One Procedure: The Nationwide Inpatient Sample. J Alzheimer's Dis. 2017;57(3):813–24. DOI 10.3233/JAD-161225

7. Eratne D, Loi SM, Farrand S, Kelso W, Velakoulis D, Looi JCL. Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. Australas Psychiatry. 2018;26(4):347–57. DOI 10.1177/1039856218762308

8. Crisóstomo GF, Menezes APS, Silva JF, Sales NJF, Agostinho PL da S, Nunes AL de F, et al. Influência da faixa etária, sexo e número de óbitos na prevalência de hospitalizações pela Doença de Alzheimer no Brasil. Ciênc e Saúde Colet. 2020;(12):21. DOI 10.22533/at.ed.87520110212

9. Santos DM dos, Pinheiro I de M, Ribeiro NMDS. Morbidade e mortalidade da doença de Alzheimer em indivíduos hospitalizados no Brasil, entre 2008 e 2018: estudo ecológico. Rev Ciênc. Méd. e Biol. [Internet]. 2019 Dec 20;18(3):314. Available from: https://portalseer.ufba.br/index.php/cmbio/article/view/34169 DOI 10.9771/cmbio.v18i3.34169

10. James BD, Wilson RS, Capuano AW, Boyle PA, Shah RC, Lamar M, et al. Hospitalization, Alzheimer's Disease and Related Neuropathologies, and Cognitive Decline. Ann Neurol. 2019;86(6):844–52. DOI 10.1002/ana.25621

11. Tiwari S, Venkata A, Kaushik A, Adriana Y, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019;Jul 2019(14):5541–54. DOI 10.2147/IJN.S200490

12. Villarejo Galende A, Eimil Ortiz M, Llamas Velasco S, Llanero Luque M, López de Silanes de Miguel C, Prieto Jurczynska C. Report by the Spanish Foundation of the Brain on the social impact of Alzheimer disease and other types of dementia. Neurol (English Ed [Internet]. 2021;36(1):39–49. Available from: http://dx.doi.org/10.1016/j.nrleng.2017.10.004

13. Mitchell SL. Advanced Dementia. N Engl J Med. 2015;372(26):2533–40. DOI 10.1056/nejmcp1412652

14. Kalamägi J, Lavikainen P, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S, et al. Predictors of high hospital care and medication costs and cost trajectories in community-dwellers with Alzheimer's disease. Ann Med [Internet]. 2019;51(5–6):294–305. Available from: https://doi.org/10.1080/07853890.2019.1642507

15. Levorato CD, de Mello LM, da Silva AS, Nunes AA. Fatores associados à procura por serviços de saúde numa perspectiva relacional de gênero. Cienc e Saude Coletiva. 2014;19(4):1263–74. DOI 10.1590/1413-81232014194.01242013

16. Da Silva MWLA, Silva JV de M, Da Silva MLA, Wanderley GS, Wanderley GS, De Lira NET, et al. A doença de alzheimer no cenário hospitalar do brasil de 2013 a 2017: aspectos epidemiológicos. Frente Diagnóstica e Ter a Neurol 2. 2020;2(1):1–7. DOI 10.22533/at.ed.5612028011

17. Lopes MA, Bottino CMC. Prevalência de demência em diversas regiões do mundo: Análise dos estudos epidemiológicos de 1994 a 2000. Arq Neuropsiquiatr. 2002;60(1):61–9. DOI 10.1590/s0004-282x2002000100012

18. Wimo A, Winblad B, Jönsson L. The worldwide societal costs of dementia: Estimates for 2009. Alzheimer's Dement. 2010;6(2):98–103. DOI 10.1016/j.jalz.2010.01.010