RESEARCH ARTICLE

Prevalence of Alzheimer's disease according to anticholinesterase drug usage from 2012 to 2017 in the state of Paraná, Brazil [version 1; peer review: 1 approved with reservations]

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Abstract

Introduction: Alzheimer's disease (AD) is a public health problem in Brazil due to the growing number of older adults in this population. Knowing the prevalence of AD in the Paraná state is essential to improve patients' quality of life. The objective of the study was to estimate AD prevalence in the state of Paraná, based on the prescription of anticholinesterases, from 2012 to 2017.

Methods: Patients diagnosed with AD, aged 60 years or over, who used Brazil's Unified Public Health System (SUS) and received AD medication from the Department of Pharmaceutical Assistance of the state of Paraná, from 2012 to 2017, were the target population of the present study. The medication data were collected from the *Computerized system management and Monitoring of Exceptional Drugs* (SISMEDEX), and the population's data were collected from the Brazilian Institute of Geography and Statistics (IBGE).

Results: The sample consisted of 52,687 patients, and the median prevalence of AD in the established period for the state was 642.6/100,000 inhabitants (0.64%). In all ages and macro-regions, women showed the highest prevalence rates. The median prevalence for women in the established period was 755.4/100,000 inhabitants (0.75%). Among men, the median prevalence was 510.2/100,000 inhabitants (0.51%). In the temporal analysis of prevalence, between 2012 and 2017, a reduction of 23% was found in the state rate. The prevalence rate of Paraná for AD is nine times lower than the Brazilian

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view

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average.

Conclusions: Paraná's prevalence rate for AD is lower than the rates of Brazil and the world, suggesting that AD is underdiagnosed in most municipalities of this state.

Keywords

Alzheimer's disease, Brazil, Prevalence, Pharmacoepidemiology, epidemiology

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Introduction

The growth of the elderly population is a worldwide phenomenon. As life expectancy rises, epidemiological changes cause risk factors for noncommunicable diseases (NCDs) to increase¹. Among NCDs, neuropsychiatric disorders must be highlighted because, in 2013, they were responsible for more than a third, 34%, of all morbidity reported in Brazil².

According to the latest report from Alzheimer's Disease International, dementia is the most common neurological disease in the elderly population. It affects 50 million people worldwide, with the number expected to triple by 2050. More than half of all people with dementia live in low- and middle-income countries, where only 10% of individuals receive adequate diagnosis³.

Among dementias, Alzheimer's disease (AD) is the most prevalent, accounting for 50–70% of cases. AD is a neurodegenerative disease that causes progressive deterioration of intellectual and routine skills, as well as cognitive impairment⁴. In Brazil, it is estimated that 6% of the 15 million people who are over the age of 60 suffer from AD^{4,5}.

The literature describes a strongly positive relationship between age and dementia. After the age of 65, the prevalence rate of dementia doubles every five years⁶. Long-term care by both the patients' family and the state becomes inevitable as the disease progresses, mainly due to the loss of patients' functional capacity. Therefore, with the increase in the elderly population in Brazil, AD represents a significant public health problem^{7,8}.

The global AD prevalence rate of people aged 60 is 3.9%, with a significant variation between continents, with a rate of 1.6% in Africa, 6.4% in North America, 7.1% in South America, 5.5% in Asia, and 9% in Europe^{9,10}. Brazilian studies suggest a prevalence of 7.1% for dementia among people over the age of 65^{2,11,12}. Considering the dementia prevalence and the high number of older adults (15 million) in 2013, it is estimated that 1.1 million people lived with this condition in Brazil¹³.

Few studies are available specifically on the prevalence and incidence of AD in Brazil. Most studies address all dementias, have a small sample size, or are developed in an institutionalized environment. Furthermore, a significant variation in the results is found, which hinders the identification of the true dementia prevalence among elderly Brazilians^{2,11,12}.

AD has no cure, and even though available medications alleviate the symptoms and delay the progression of the disease, current therapy is far from being satisfactory¹⁴. The drug treatments currently available for AD are acetylcholinesterase inhibitors (AChEIs), such as rivastigmine, galantamine and donepezil, and N-methyl-D-aspartate (NMDA) receptor antagonist, such as memantine¹⁵.

AChEIs are the primary drugs used to treat AD. Since 2002, Brazil counts on the Assistance Program for Alzheimer's Disease Patients (PAPDA), which aims to address 50% of AD patients throughout the country¹⁶. The government offers, through Brazil's

Unified Public Health System (SUS), free treatment for patients with AD, according to the Clinical Protocol and Therapeutic Guidelines (PCDT) - Alzheimer's Disease. The PCDTs are made by technical-scientific consensus and aim at rationalizing medical prescription and dispensing, through previously established diagnostic criteria, with recommended treatments (drugs and their respective dosages) and mechanisms for monitoring effectiveness¹⁷.

Medicines are highly relevant inputs to establish policies and priorities adjusted to the population's health needs but are rarely used in prevalence studies¹⁵. The information resulting from the use of specific drugs is predictably more reliable since drugs used in the treatment of cognitive symptoms follow specific protocols from the Brazilian Ministry of Health and can only be applied in the treatment of AD¹⁸.

In Brazil, AD is not part of the national list of notifiable diseases, therefore there is no national and official registry of patient cases in the country¹⁹. The only official references related to AD in the country are the registration of medicines dispensed for the disease, which is provided by SUS, and the AD death certificates that are registered in the Ministry of Health's Mortality Information System (SIM).

Data related to drugs dispensed by SUS may estimate cases of AD in the state since the control of patients in this dispensation program is individualized and rigorous. The patient is diagnosed based on ICD-10 (**International Classification of Diseases, 10th Revision**), which reduces diagnosis errors²⁰.

In Brazil, there are several publications on AD; however, few are about the prevalence of the disease in a large sample of the population, and none are specific to the state of Paraná. The lack of national and state data triggers a deficiency in the understanding of the disease's epidemiological profile in the country and the state, despite its well-known impact on public health.

The present study aimed to present the historical estimate of AD prevalence in the state of Paraná, based on the prescription of anticholinesterases among SUS users, from 2012 to 2017.

Methods

Ethical statement

The present study was approved by the Research Ethics Committee of Midwest State University of Paraná (UNICENTRO), under number 2.334.461/2017. The requirement for patient consent was dismissed by the ethics and research committee because this study uses secondary only data.

Study design and population

A cross-sectional, retrospective, and descriptive study, with a quantitative approach, was performed in the state of Paraná from 2012 to 2017. The study population consisted of patients diagnosed with AD, users of SUS, in the state of Paraná and who received medication for AD in the studied period. Patients who were diagnosed based on PCDT for AD and had one of the following ICD 10 diagnostic codes were included; G30.0, G30.1, and G30.8.

Only patients who withdrew medication through the SISMEDEX program were included in the present study. Therefore, only data from the population over 60 years old who received their medications from SUS (free of charge) during the study period were analyzed. People with AD who privately purchased their drugs were not counted in this study. Also, patients under the age of 60 or with different ICD from those determined in the inclusion criteria who withdrew medication through the SISMEDEX program, were excluded from the study.

A sample size calculation was not performed, since all 399 municipalities in Paraná were studied, as well as all patients over 60 years old, respecting the study inclusion criteria. The cut-off age, 60, was determined based on the majority of prevalence studies.

Data variables

The following SISMEDEX system variables were collected; patient's gender, city and age, the medication that was interrupted and used for AD, and the health region to which the patient belongs. The data on this system are filled by pharmacists from the health region responsible for dispensing the drugs. Estimates of population by sex, age group (>60 years) and year used to calculate the prevalence coefficients were obtained from the [Brazilian Institute of Geography and Statistics \(IBGE\)](#), calculated on July 1st of each year.

The results of the study are separated by age groups and macro-regions of Paraná; the macro-regions comprise the 22 health regions that are governmental divisions. Regional health encompasses nearby municipalities that share as SUS health structures.

Data analysis

Initially, a description of the main characteristics of the sample was performed for data analysis. The AD prevalence of each year was estimated by dividing the number of cases of AD in patients over 60 years old in Paraná (numerator) by the population over 60 years old residing in Paraná during the same period (denominator), multiplied by 100,000, with the result expressed per 100,000 inhabitants.

The descriptive analysis of the data included frequency distributions for categorical variables as well as measures of central tendency (mean, median) for continuous variables. The chi-square test was used to assess differences in proportions. Differences were considered statistically significant at $p < 0.05$.

The data were analyzed using the IBM SPSS Statistics v.20.0 computer program. Armonk, New York: IBM Corp.

Results

During the study period, 65,494 patients registered in SISMEDEX who received IChE drugs were identified. The final sample consisted of 52,687 patients diagnosed with AD using IChE in the state of Paraná in the years 2012 to 2017²¹. This

sample served as a basis for determining the prevalence of the disease according to the year and patients' gender and age group.

The mean age of the sample was 79.89 ± 8.1 , in which female cases represented 63.5% ($n = 33,465$) and male cases, 36.5% ($n = 19,222$).

All patients received drugs dispensed by the health regions of Paraná. 12,807 patients were excluded from the study, 1,239 patients being under 60 years old, and 11,568 patients for having multiple records. SISMEDEX generates a new patient in the system every time a medication or its' dose changes, or when the dispensing address is altered; therefore, some records are multiplied. This issue was corrected by selecting patients using their initial registration number in the system and not by the type of medication dispensed, change in dosage, or delivery address.

Regarding the sample's ICDs, the following percentages were found; 62% ($n = 32,666$) for G30.0 (early onset Alzheimer's disease), 33% ($n = 17,386$) for G30.1 (late onset Alzheimer's disease) and only 5% ($n = 2,635$) for 30.8 (other forms of Alzheimer's disease).

The median overall prevalence of AD among the elderly in the state of Paraná from 2012 to 2017 ([Table 1](#)) was 642.6/100,000 inhabitants (0.64%). Overall, the prevalence in females was 41% higher, at 755.4/100,000 inhabitants (0.75%) and 510.2/100,000 inhabitants (0.51%) among men ([Table 1](#)).

When separated by age groups, the median results of AD prevalence in the state of Paraná showed a trend of progression, associated with age, regardless of gender. The median prevalence of AD in both genders aged 60–69 was lower than 1% (107.4/100,000 inhabitants). These results contrast with the median prevalence of AD in patients over the age of 80, in both genders, which was higher than 2%.

When compared to the prevalence in males in the same age groups, the prevalence of AD in women aged 60 to 69, 70 to 79 and 80 or over was 29%, 28%, and 41% higher, respectively. Differing between genders, in men over 80 years old, the median prevalence was 2054.0/100,000 inhabitants (2.05%), and for women in the same age group, the prevalence was 2903.7/100,000 inhabitants (2.90%).

The median prevalence of AD among the elderly in the state of Paraná during the period studied vary according to the states' macro-regions ([Figure 1](#)). Fewer cases were found in the east macro-region of the state: 401.6/100,000 inhabitants, which is 60% lower than the median of cases in the entire state in the same period. In contrast, when compared to the state's median, the northwest macro-region showed a rate that is 96% higher, with 1235.5/100,000 inhabitants. West and north macro-regions presented a rate of 642.6/100,000 inhabitants and 614.5/100,000 inhabitants, respectively. The northwest macro-region has the highest number of cases in the state, showing a prevalence

Table 1. The prevalence rate of Alzheimer's Disease (/100,000 inhabitants) among age groups and genders in Paraná from 2012 to 2017.

Gender	Age group	Year						Median
		2012	2013	2014	2015	2016	2017	
Female	60–69	624.0	617.0	603.0	562.0	563.0	521.0	138.2
	70–79	2109.0	2105.0	2084.0	1981.0	1901.0	1792.0	902.0
	80 +	2972.4	3009.5	2971.5	2835.8	2771.0	2617.5	2903.7
	Total	810.3	801.6	779.9	731.0	699.3	649.0	755.4
Male	60–69	436.0	426.0	411.0	391.0	384.0	387.0	107.4
	70–79	1309.0	1276.0	1313.0	1281.0	1288.0	1214.0	703.3
	80 +	2270.5	2201.0	2128.6	1979.5	1932.3	1831.8	2054.0
	Total	566.2	541.4	527.5	493.0	477.4	447.0	510.2
General total		698.4	681.4	663.6	621.5	597.3	556.1	642.6

Figure 1. Disease prevalence rate (/100,000 inhabitants) over the age of 60 of both genders in Paraná's macro-regions, from 2012 to 2017.

rate three times higher than the east macro-region, which presents the lowest number of cases in this period.

As shown in [Figure 1](#), all macro-regions of Paraná presented the highest prevalence of AD in 2012, with 698.4 cases/100,000 inhabitants, with a decline in rates within the following years, showing a 23% reduction in 2017, with 556.1 cases/100,000 inhabitants. Variation was found in the north macro-region, showing stability for the female gender in the last three years analyzed. In the same macro-region, male patients showed prevalence stability during the first three years studied, presenting a decline in 2015 and, once again, stability in 2016.

AD prevalence rates are shown in [Figure 2](#), [Figure 3](#), and [Figure 4](#) (per 100,000 habitants), according to age group, year, patient's gender, and Paraná macro-regions.

The prevalence of AD among 60–69 years old patients is shown in [Figure 2](#). The northwest macro-region presented the highest number of cases for both genders, with a median prevalence of 287.8/100,000 inhabitants and 225.4/100,000 inhabitants for women and men, respectively. In general, rates declined for this age group over the years studied, showing occasional increases, as in 2016 in the northwest macro-region among women, and in the north macro-region in 2013 among women and in 2014 among men.

The prevalence of AD among 70–79-year-old patients is shown in [Figure 3](#). Among this group age, the northwest macro-region demonstrated the highest number of cases in both genders during the period studied, with a median prevalence of 1801.9/100,000 inhabitants and 1218.1/100,000 inhabitants for women and men, respectively. A decline in AD prevalence from 2012 to 2017

Figure 2. Alzheimer's disease prevalence rate (/100,000 inhabitants) of ages 60 to 69, both genders, in Paraná's macro-regions, from 2012 to 2017.

Figure 3. Alzheimer's disease prevalence rate (/100,000 inhabitants) of ages 70 to 79, both genders, in Paraná's macro-regions, from 2012 to 2017.

was observed, with some exceptions in specific years and intensity variations according to the macro-region.

In the age group of patients aged 80 and over (Figure 4), the highest prevalence rates in the state were found for both genders

and all macro-regions during the period studied. When compared to other age groups, the decline in AD prevalence was lower for patients aged 80 and over, with higher fluctuations over the years studied. For women, rates declined in the east and west macro-regions and fluctuated in the northwest and north

Figure 4. Alzheimer's disease prevalence rate (/100,000 inhabitants) over the age of 80, both genders, in Paraná's macro-regions, from 2012 to 2017.

macro-regions. Among men, rates declined over the years studied, but in the north macro-region, a decrease was observed in 2016, with a subsequent increase in 2017.

Discussion

In the present study, the prevalence of AD in the state of Paraná between the years 2012 and 2017 was assessed based on data collection of patients with a confirmed diagnosis who used the government's drug treatment program. Thus, the prevalence of AD described for patients undergoing treatment was 642.6/100,000 inhabitants (0.64%). When comparing the results of the present study and the prevalence rates of AD in other Brazilian studies, similarities were found. Nitri *et al.* (2004) demonstrated a prevalence rate of 0.77% in Catanduva-SP¹². However, other studies demonstrated higher AD prevalence rates. Three studies performed in the city of São Paulo showed a prevalence of 4.9%²², 5.1%²³, and 6.8%²⁴.

A recent systematic review on the prevalence of dementia in Brazil showed a prevalence ranging from 5.1% to 17.5%, in which AD was the most prevalent and responsible for 60% of cases⁵. The variations in prevalence may be attributed to differences between the population, the number of samples and the methods applied in each study. It is also important to highlight that the Brazilian studies used for the comparison took place in the southeast region of the country, and the majority were based on institutionalized individuals.

Worldwide prevalence data for AD, published in 2010 by the 10/66 Dementia Research Group, demonstrated the differences in the prevalence of dementia among developing countries. The

rate of AD in Cuba was 11%, in Mexico 7.3%, in India 7.5%, in Africa 5.85%, and China 7.2%²⁵.

International studies also showed higher prevalence rates than those reported in the present study, which can be attributed to the lack of diagnosis and treatment for AD in Paraná. Only 14% of developing countries have reports containing the number of people with AD being diagnosed and treated. Studies suggest that up to 90% of people with dementia in low- and middle-income countries are unaware of their condition^{3,15,25}.

Table 1 reports the cases of AD by age group, and as age increases, the number of patients also increases. The age group of 80 years old and over showed 68% of AD cases found in the study. These data are congruent with Brazilian and international population studies in which it is verified that the prevalence of AD increases almost exponentially with age. Therefore, among the most advanced age groups, the most significant number of patients was found in the present study^{3,15}. Literature reports that dementia prevalence doubles approximately every five years, matching the data from the present study in which AD prevalence increased by an average of 2.5 times every five years until the age of 79^{15,25,26}. The demographic trends of the country, characterized by population aging, contribute to the increase of AD cases over the years, as age is the leading risk factor for its development^{27,28}.

The results of the present study also suggest a tendency to a higher prevalence of AD among women in Paraná (**Table 1**), with a median coefficient of 755.4/100,000 inhabitants (0.75%) among women and 510.2/100,000 inhabitants (0.51%) among men.

The median overall prevalence rate was 48% higher for women than for men. This result may be justified by women's higher life expectancy, the prevalence of older women in the sample, the feminization of aging, and the fact the majority of those who use health services are women^{29–31}.

When comparing men and women by age group (Table 1), once again, the results demonstrated the highest rates of AD among women regardless of age group. These results also match the data presented in the demographic and epidemiological profile of users of high-cost drugs in SUS, in which women showed higher rates of AD drug consumption, at 1.72% against 1.36% for men³².

In 2010, the population pyramid in Paraná had a barrel-like shape, characteristic of populations in the aging process, with a narrow shape on the base and a wider shape on the top, particularly among women due to over-mortality of men at advanced age³³. Within this panorama, a phenomenon called the feminization of aging is observed. According to the World Health Organization (WHO), older women are living longer than men almost everywhere in the world³⁴.

Men's average life expectancy is 69.1 years old, while women's is 73.8 years old, a difference of 4.7 years. In Brazil, this difference in favor of women averages seven years³⁵. There are several explanations for greater female longevity. One of them is women's attitude towards health/illness and health service, as they do more tests and routine medical consultations. There are also biological differences between the genders, such as protective factors related to female hormones. Also, there are differences in lifestyle; men are generally more exposed to risks at work, and alcohol and tobacco consumption³⁶.

The prevalence of differences between men and women may vary regionally within the state, due to the heterogeneity of the age profile. Although women showed higher rates than men, differences between genders were not significant, and consequently inconclusive. Therefore, it is not inferred that being a woman implies a higher chance of developing AD^{11,12}.

When the results were separated by age groups, and macro-regions of Paraná, more considerable differences were found. The macro-regions comprise the 22 Health Regions of the state, and they were used in this study to facilitate comparisons. The highest median prevalence rate for AD was identified in the northwest, with 1235.5/100,000 inhabitants, and the lowest rate was found in the east, with 401.6/100,000 inhabitants. The ten largest cities in Paraná concentrate 41% of the entire population of the state; 51.6% of people live in municipalities with more than 100,000 inhabitants³⁷. Despite the large population concentration in the east region of the state (Curitiba and the coast), the population of Paraná stands out for the existence of a significant number of medium-sized cities in the state's countryside, a fact that regionalizes the demographic polarization³⁷.

The intra-state analysis reveals heterogeneity among the municipalities of Paraná, which demonstrated a human development

index (HDI) ranging from 0.546 in Doutor Ulysses city (lowest in the state) to 0.823 in Curitiba (highest in the state), both cities in the east macro-region³⁸. A total of 39 municipalities in the state of Paraná present low HDIs (<0.658) (10%). Among these municipalities, the majority (25) are in the east macro-region of the state. Associating the hypothesis reported in Table 1 with the socio-economic aspects of the state, the present study suggests that the prevalence of AD is lower in cities with a lower HDI²³. The northwest macro-region has a large number of cities with the highest HDIs of the state, which generally provides a better education, health, and life quality - factors that protect against dementia. According to the literature review of Sharp and Gatz (2011), the relationship between schooling and risk of dementia was more significant in developed regions with a higher HDI than in developing regions, matching with the findings of the present study³⁹.

In general, the largest municipalities with the highest HDI also have the best information management in health and medical care, consequently producing more accurate and reliable information^{40,41}. Thus, the possible explanation for a higher prevalence of AD in municipalities with a higher HDI may be associated with better investigation and diagnosis of AD cases⁴⁰. Mendonça *et al.* (2016) inferred that small cities, generally located in more isolated geographical areas, with greater social and economic vulnerability, are overlooked by doctors, which hinders AD diagnosis and treatment⁴¹.

The index of the older adults in Paraná state from 2016 to 2019 relates the population number of older adults (≥60 years old) to those of children and young people (≤15 years old). These two extreme segments of the disparate age pyramid allow a more precise measure of comparability among the municipalities of the state. The east macro-region has the most significant number of cities in Paraná with a low rate of older adults. In this macro-region, an average of less than 49 older adults per 100 children and young people is found, characterizing a young population³⁸. This average correlates with the literature, in which the prevalence of AD increases with the increase of age^{1,42}. The opposite occurs in the northwest macro-region, where most cities show proportions close to 70 older adults for every 100 children and young people, characterizing an aging population, contributing to a greater number of cases of AD in this region.

Risk factors associated with diabetes mellitus (DM) have been linked, in several observational studies, to the development of dementia since the early 2000s⁴³. A worldwide trend suggests that the increase in AD risk occurs by a direct link between glucose dysregulation and neurodegeneration. Authors consider AD as type 3 diabetes mellitus, due to its similarity to histopathological, molecular, and biochemical anomalies^{43–45}.

Correlating the prevalence of AD with diabetes mortality, between 2004 and 2014 the rate of deaths by DM in the state was 32.0 deaths/100,000 inhabitants, with a higher incidence in women⁴⁶. Twelve health regions from Paraná presented higher DM mortality rates than the state, and three of them are in

the northwest macro-region. This is in contrast to the east macro-region, in which most of the health regions present AD mortality rates below the state average⁴⁵. Epidemiological evidence links these two diseases, Shinohara and Sato (2017) reported that the risk of developing AD is higher among people with DM than in the general population, especially in the eastern populations⁴⁷.

Some limitations of the present study should be highlighted. The sample consists of patients linked to SUS, which impedes the generalization of the results for the entire population. Additionally, this retrospective study refers to secondary data, which was originated with an administrative purpose and made it difficult to obtain more detailed information. Some clinical information was not required while filling out the database, such as the starting date of medication usage; therefore, this data could not be collected and used in the present study. As an example of a lack of information, more than half (62%) of the patients studied were diagnosed with ICD 30.0, early-onset AD. This number of diagnoses conflicts with the literature since early-onset AD (before age 65) affects 6–7% of the population, usually with family background and an autosomal dominant transmission pattern^{12,48}. Inaccurate AD diagnosis triggers a false epidemiological profile, due to incorrect or incomplete database, distorting and altering the epidemiological reality⁴⁹. Therefore, the correct input of ICD codes in the SISMEDEX/PR database must be reviewed before such results can be inferred.

Also, the scarcity of scientific evidence and the difficulty of accessing information of this nature in Brazil is highlighted. Currently, no reliable information that addresses the dispensation

of medication by the private sector is available, making it impossible to compare it with the public sector. Nevertheless, the present study shows that governmental information systems are essential secondary data sources, and they should be used mainly due to the low cost and availability of information over a long period. Data presented in this article is vital for prevalence studies; this information has never been published, and it guides further analysis.

Conclusions

As the population ages, the number of AD cases in Paraná increases during the studied period. Besides, Paraná's prevalence rate for AD was nine times lower than the national rate average. This result suggests that AD is still underdiagnosed in most municipalities in Paraná.

The information presented was obtained from 52,687 patients, and it can provide subsidies for planning actions related to AD, and most important, collaborating to improve the quality of primary care. Also, an extended national assessment could be performed based in the present study, since the reality and needs of Brazil states are similar.

Data availability

Underlying data

Harvard Dataverse: Prevalence of Alzheimer's disease according to anticholinesterase drugs usage from 2012 to 2017 in the state of Paraná, Brazil. <https://doi.org/10.7910/DVN/FE2G6A>²¹

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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This is a retrospective pharmacoepidemiological study on the use of acetylcholinesterase inhibitors (AChEI) among older residents of Paraná, Brazil. The topic is of importance due to Brazil's heavily increasing older population and due to the apparent lack of studies concerning the subject. The authors have framed the research as a study on the prevalence of Alzheimer's disease (AD) in the population, but I disagree with this framing for multiple reasons. However, despite obvious limitations, the study offers interesting data on drug utilization. Here are some of the issues I would wish the authors to comment on:

- As I mentioned, the study is framed as a study on the prevalence of AD. The study suggests a low prevalence of AChEI in the population, which may be considered somewhat unsurprising. Could the authors explain why they suggest using drug use as a proxy for disease prevalence in this case? I would suggest reframing this as a drug utilization study throughout the manuscript.
- Could the authors describe the diagnosis process? The manuscript mention that the diagnosis criteria are based on international standards, but these standards are not referenced. In the discussion, the authors write that the diagnosis is confirmed, but there is no mention of how this confirmation is made earlier in the text.
- Why is memantine not investigated in this study? If available, it should be included in the analyses. If not, it should be discussed as a limitation.
- Despite obvious pitfalls in using AChEI prevalence as a proxy for AD prevalence, the authors make detailed hypotheses on biological reasons for the findings. This is problematic since the analyzed sample of people with probable AD is likely to be very biased. I would suggest removing the discussion related to glucose deregulation from the discussion section completely. Moreover, I suggest the authors add to the limitation section that this sample is likely to be a small part of the people with AD in the Paraná's population.

- Related to the previous comment, the authors refer to the disproportionality of early AD as inaccurate diagnoses. Could the authors comment on why this theory would be preferable to sampling bias?
- Are there previously published estimates as to how large a part of the older population uses the SUS? If not, this should be discussed as a limitation in the discussion.

Minor comments:

- Please refer to AChEIs systematically with the same term throughout the manuscript.
- Please refer to gender-related terminology systematically, i.e., use “gender” instead of “sex” and “men and women” instead of “males and females”.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoepidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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