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ORIGINAL ARTICLE

Antidepressant use and stroke or mortality risk in the elderly

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Abstract

Background and purpose: Current evidence on antidepressant-related stroke or mortality risk is inconsistent. Because the elderly have the highest exposure to antidepressants, the aim was to quantify their association with stroke and mortality risks in this vulnerable population.

Methods: Persons over 65 years old and registered in the Information System for Research in Primary Care of Catalonia during 2010–2015 comprised the study population. Antidepressant exposure was categorized into current-users, recent-users, past-users and antidepressant non-users (controls). The effect of antidepressant exposure on stroke or death, whichever came first, was analyzed by Cox regression adjusted for established risk factors.

Results: Of the 1,068,117 participants included, 20% had antidepressant reimbursements during follow-up, 17% had a stroke and 3% died. The risk of experiencing stroke or death was higher in antidepressant current-users (hazard ratio [HR] 1.04; 95% confidence interval [CI] 1.02–1.06), recent-users (HR 3.34; 95% CI 3.27–3.41) and past-users (HR 2.06; 95% CI 2.02–2.10) compared to antidepressant non-users. Antidepressant current-use was associated with increased stroke (HR 1.56; 95% CI 1.50–1.61) but decreased mortality risk (HR 0.93; 95% CI 0.91–0.94). During antidepressant recent-use and past-use, both stroke and mortality risks were significantly increased compared to no antidepressant use.

Conclusions: Antidepressant use may be associated with increased stroke risk in the elderly. When using antidepressants in this population, the potential risks should be considered.

KEYWORDS
aged, antidepressive agents, mortality, pharmacoepidemiology, stroke

INTRODUCTION

Antidepressant use has been rising in developed countries [1]. In Catalonia, antidepressant consumption increased by 22% between 2007 and 2011 [2]. The prevalence of antidepressant consumption in the Spanish elderly population significantly increased from 4% in 2003 to 8% in 2009 [3]. Age was positively correlated with the prevalence of antidepressant use in all European databases analyzed in many pharmacoepidemiology studies [1].

Although the elderly have the highest exposure to antidepressants, limited data are available to justify their use in this vulnerable population. They are usually excluded from randomized controlled trials [4] and meta-analyses show small effect sizes for antidepressants compared to placebo with no substantial efficacy difference

between antidepressant classes [4–6]. Considering their favorable tolerability, guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as first-line therapy for depression, reflecting results from randomized controlled trials in younger adults [6]. Age-related polypharmacy, multimorbidity and physiological changes affecting drug metabolism and action in the elderly make such an extrapolation problematic [4].

Stroke is the second cause of death worldwide [7]. Each 10-year increase in age doubles the annual stroke risk [8]. SSRIs and other antidepressants, which include but are not limited to serotonin–norepinephrine reuptake inhibitors (SNRIs), were associated with higher risk of stroke in a geriatric population, whereas tricyclic antidepressants (TCAs) were not [9]. Yet, another study had contradicting conclusions: SSRIs, but not TCAs, were protective against stroke [10]. In terms of mortality, elderly men from a French cohort were more likely to die if they were on antidepressant medication versus not on antidepressant medication [11]. These results were replicated in Australia [12]. A database study found similar results, without differentiating the sex effect [9]. However, current antidepressant treatment was found to reduce mortality in a user-only study analyzing all age groups [13].

With increasing life expectancy and reduced fertility, the proportion of the population aged over 65 years is projected to increase from 19% in 2020 to 27% by 2050 and to 30% by 2100 in developed countries [14]. Therefore, elucidating the relationship between common exposures and serious health issues within this population is crucial. Our primary objective was to estimate the risk of stroke or mortality related to antidepressant use compared to no antidepressant use in the elderly. As subgroup analyses, this risk was assessed for separate antidepressant classes. The aim was also to separately quantify the risks for ischaemic stroke, hemorrhagic stroke, unspecified stroke, death and fatal stroke.

METHODS

Study design

An observational cohort study was conducted, including persons aged over 65 and registered in the Information System for Research in Primary Care (SIDIAP). Ethics Committee approval was received from the University Institute for Primary Care Research Jordi Gol Clinical Research on 12 May 2016. Informed consent from the participants was not necessary because of the retrospective nature of the anonymized data collection. This study is registered in the European Union Post-Authorization Studies Register (number EUPAS19188) [15].

Data source

The Information System for Research in Primary Care database contains electronic medical records of persons receiving health services from the Catalan Institute of Health (CIH), comprising approximately 74% of the Catalan population, Spain [16]. The analysis dataset, retrieved in 2017, consisted of variables related to demographics, diagnoses (International Classification of Diseases [ICD] 10), smoking and number of practitioner visits from primary care records on a daily basis. Monthly drug reimbursements (Anatomical Therapeutic Chemical [ATC]) by the National Health System dispensed to outpatients with prescriptions from CIH physicians were available without a specific date. The date of death from the Health Department was linked to the demographics table. The dataset covered the period from 1 January 2009 to 31 December 2015.

Study population

Persons registered in SIDIAP between 1 January 2010 and 31 December 2015 were eligible if they were born between 1900 and 1950. Persons who exited the CIH healthcare system during the study period were considered ineligible to prevent potential duplicates due to reentry.

The cohort was formed from eligible persons who entered the cohort in the initial month they met the inclusion criteria. Persons were included when they were over 65 years old. Participants were included if they were registered in SIDIAP for at least 12 months before inclusion, provided they had at least one primary care visit [17] and no antidepressant reimbursement during this period. The cohort was followed until death or end of the study period.

Exposure

The follow-up time was divided into antidepressant treatment episodes based on the reimbursement data. The current-use episode was formed by joining consecutive months of antidepressant reimbursement including 1 month gaps (the grace period) with no reimbursement. Switching to different antidepressant agents was also allowed. When a current-user stopped antidepressant treatment, the first 2 months following the grace period were categorized as recent-use. Past-use was defined as the 9 months immediately following recent-use. Consecutive months without antidepressant reimbursement at the current month and for at least 12 preceding months were joined to create a no antidepressant use episode. Graphical presentation of the treatment episode construction is available online in Appendix S1. For subgroup analysis, the antidepressants reimbursed during a use episode were categorized into the following classes: TCAs, SSRIs, antidepressants other than TCAs or SSRIs, and multiple (drugs from multiple antidepressant classes during a single use episode).

Outcomes

The outcome was detected from the fields of diagnoses and the death registry in the SIDIAP dataset. Primary outcome was the

composite of stroke and all-cause mortality (as date of death) to account for competing risks [18]. For secondary analyses, stroke was categorized as ischaemic (I63), hemorrhagic (I60–I62) or unspecified (G46, I64). Stroke was considered fatal if death occurred within 30 days.

Covariates

Age, sex and urbanity (demographic variables) were assessed at cohort entry. Smoking status was determined during the study period. The number of primary care visits during the year before episode-start was used as a proxy for health-seeking behavior. Comorbidities and comedications that are established or possible risk factors for stroke or antidepressant use were selected. Comorbidities were collected from primary care diagnoses records any time before antidepressant treatment episode-start. Comedication reimbursements were determined during 6 months before the episode-start. All covariates are described in Table 1. Lists of all the variables and their definitions based on ATC or ICD codes are available online in Appendix S1.

Statistical analysis

Time to the composite outcome was analyzed by the time-varying Cox proportional hazards model. The composite outcome was chosen as the main outcome because both death and stroke are clinically relevant. Exposure was the time-dependent variable. No antidepressant use episode was the reference category. The effect estimates were adjusted for time-constant recruitment month, demographic variables and smoking. Further adjustment for comorbidities, comedications and number of primary care visits was employed by allowing them to be updated whenever a person changed from one exposure episode to another. In subgroup analyses, use episodes of individual antidepressant classes were compared to the episodes of non-use.

When the composite outcome was the dependent variable, a person's observation was terminated if the person experienced stroke or death. For the analysis of stroke, a person's observation was censored on the date of death, a cause-specific hazard model or at the end of the study. For the analysis of death, the observations of persons who survived up to the end of the study were censored. Following recruitment, persons with missing urbanity level were excluded from the analysis because their proportion in the total cohort was negligible.

An alpha level of 0.05 was used in the Wilcoxon rank-sum test, the chi-squared test and the proportion test to compare baseline characteristics. Effect sizes were reported as crude incidence rates per 1000 person-years and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using SAS 9.4.

Various post hoc sensitivity analyses were performed to address and explore the effects of the data source and our assumptions on the results. These were (1) updating covariates regularly instead of only at episode changes; (2) the effect of potential misclassification of stroke events that occurred during the initial month of current-use due to the level of information on dispensations being to the month rather than to the date; (3) if lacking data on inpatient medications would explain the observed results; (4) if drugs other than antidepressants showed a similar trend in terms of the results; (5) the effect of conceptualizing the outcome with a subdistributional hazards model (Fine and Gray) rather than a cause-specific hazards model; (6) if combining SSRIs with SNRIs to form a single group targeting the serotonin reuptake mechanism and considering acetylsalicylic acid as an independent comedication for adjustment rather than as part of other comedication groups would change the results; and (7) if multiple imputation of missing urbanity level rather than complete-case analysis would change the results. Details of the sensitivity analyses are available online in Appendix S1.

RESULTS

From 1,307,316 eligible persons, 1,069,121 persons were recruited the first month that they met the inclusion criteria (Figure 1). From these, 1004 (0.09%) were further excluded because of missing urbanity level, leaving 1,068,117 (82% of 1,307,316) persons in the analysis cohort.

Of the final cohort, 212,621 persons (20%) had at least one (ever-users) and 855,496 (80%) had no antidepressant reimbursement (never-users) during follow-up. Baseline characteristics are presented in Table 1. At recruitment, ever-users were older, predominantly female, more likely to be non-smokers, had more primary care visits during the previous year, and were more predisposed to stroke risk factors, compared to never-users. There were 4,303,527 person-years in no antidepressant use, 264,476 person-years in current-use, 47,963 person-years in recent-use and 98,459 person-years in past-use episodes.

During follow-up, 19% of the participants experienced the composite outcome, 17% died, and 3% experienced a stroke, of which 3% were fatal. Of the stroke events, 8% were hemorrhagic, 17% were ischaemic, whereas the type was unspecified in 75%. Crude incidence rates of death and stroke were significantly higher in use episodes than in the no antidepressant use episode. Amongst participants on antidepressants, 60% were using SSRIs, 8% were using TCAs, 25% were using an antidepressant other than SSRIs or TCAs, and 7% were using antidepressants from more than one class in a single episode. Crude outcome statistics and unadjusted effect estimates are available in Appendix S1.

In the fully adjusted analysis (Table 2), risk of composite outcome during antidepressant current-use was significantly higher (HR 1.04; 95% CI 1.02–1.06) than during no antidepressant use. The composite outcome was even more likely during recent-use (HR 3.34; 95% CI 3.27–3.41) and past-use (HR 2.06; 95% CI 2.02–2.10). Risk of death was significantly lower during antidepressant current-use (HR 0.93; 95% CI 0.91–0.94) than no antidepressant use. Stroke risk was higher during antidepressant current-use than during no antidepressant use (HR 1.56, 95% CI 1.50–1.61) and gradually decreased in recent-use

TABLE 1 Baseline characteristics

Characteristic	Ever-users	Never-users	*p* value
Number of people	212,621	855,496	
Age (years), median (interquartile range)	74.8 (68.3–80.8)	70.4 (65.0–78.3)	<0.0001[a]
Sex			
Female	67%	50%	<0.0001[b]
Urbanity			
Rural	19%	20%	<0.0001[b]
Smoking			
Current smoker	15%	20%	<0.0001[b]
Ex-smoker	10%	13%	
Non-smoker	73%	63%	
Missing	3%	4%	
Primary care visits, median (interquartile range)	7 (4–12)	5 (3–9)	<0.0001[a]
Comorbidities			<0.0001[b]
No comorbidities[c]	8%	12%	<0.0001[d]
Atrial fibrillation	7%	6%	<0.0001[d]
Cardiovascular diseases	68%	62%	<0.0001[d]
Chronic kidney diseases	7%	6%	<0.0001[d]
Chronic lower respiratory diseases	9%	8%	<0.0001[d]
Coagulation/platelet defects	1%	1%	0.45[d]
Dementia	3%	2%	<0.0001[d]
Diabetes	22%	21%	<0.0001[d]
Diseases of the digestive system	0.5%	0.6%	<0.01[d]
Lipidemia disorders	45%	42%	<0.0001[d]
Mental and behavioral disorders	43%	32%	<0.0001[d]
Neoplasms	14%	13%	<0.0001[d]
Nervous system diseases	5%	3%	<0.0001[d]
Neuropathic pain and fibromyalgia	3%	2%	<0.0001[d]
Pneumonia	3%	3%	0.69[d]
Stroke	6%	4%	<0.0001[d]
Transient cerebral ischaemic attacks	2%	2%	<0.0001[d]
Comedications			<0.0001[b]
No comedications[e]	11%	18%	<0.0001[d]
Analgesics	50%	36%	<0.0001[d]
Anti-dementia drugs	3%	2%	<0.0001[d]
Anti-inflammatory and antirheumatic drugs	37%	28%	<0.0001[d]
Antipsychotics	4%	3%	<0.0001[d]
Antithrombotic drugs	31%	27%	<0.0001[d]
Systemic corticosteroid use	5%	4%	<0.0001[d]
Drugs of cardiovascular system	72%	66%	<0.0001[d]
Hypoglycemics	18%	16%	<0.0001[d]
Hypnotics and sedatives	40%	20%	<0.0001[d]

[a]Wilcoxon rank-sum test.

[b]Chi-squared test.

[c]Patients with none of the selected comorbidities.

[d]Single proportion test.

[e]Patients with none of the selected comedications.

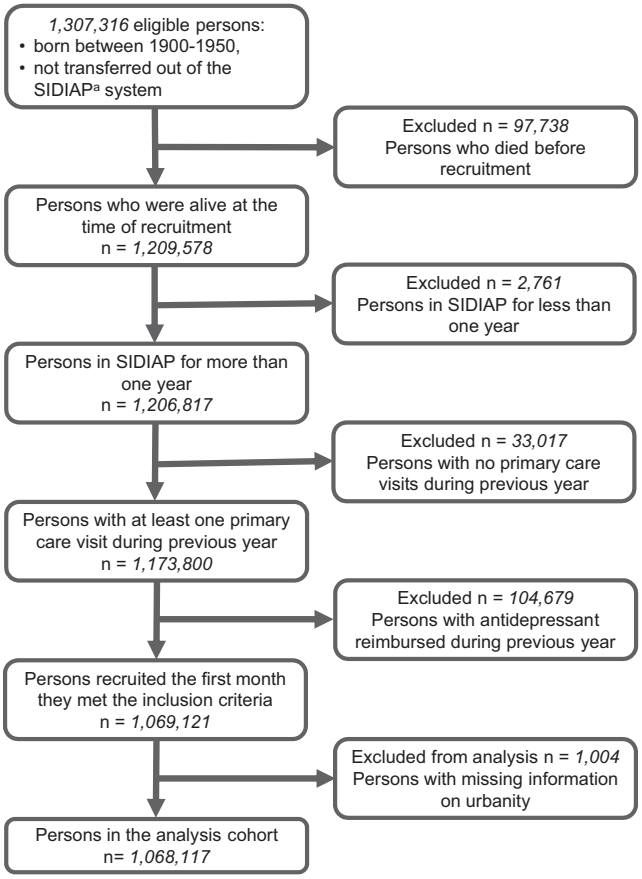

FIGURE 1 Flow-chart with final reason for exclusion. [a]SIDIAP, Information System for Research in Primary Care

(HR 1.45; 95% CI 1.33–1.58) and past-use (HR 1.21; 95% CI 1.13–1.30) but remained significant.

Compared to no antidepressant use, current- and recent-use were associated with increased risk of not only fatal stroke (HR 1.31; 95% CI 1.09–1.59) but also all stroke subtypes (ischaemic, hemorrhagic and unspecified). The simultaneous occurrence of hemorrhagic and ischaemic stroke was not analyzed because of an insufficient number of events ($n = 16$).

Analysis of the composite outcome risk stratified by antidepressant class (Figure 2) revealed significantly decreased risk for current-use of the TCAs, SSRIs and multiple antidepressants categories but significantly increased risk for the class of other antidepressants(HR 1.21; 95% CI 1.18–1.25) compared to no antidepressant use. In contrast, antidepressant recent-use and past-use increased this risk significantly. The highest risk of composite outcome was associated with the use of multiple antidepressants (more than 1.5 times compared to all antidepressants during recent-use and past-use), whilst TCAs showed the lowest risk in all categories of use episodes.

A pattern similar to that of the composite outcome is observed in the analysis regarding the isolated outcome of death (Figure 3). Use of SSRIs or the class of other antidepressants significantly increased stroke risk compared to no antidepressant use in all exposure windows (Figure 4). Although stroke risk was high during TCA current-use, it became non-significant during recent-use and past-use episodes. Low numbers of fatal stroke events did not allow the comparison of antidepressant classes.

Sensitivity analyses

The assumptions of and the results from the main analysis were robust to updating covariates regularly instead of only at episode changes (sensitivity analysis 1), considering SSRIs and SNRIs as a single group and acetylsalicylic acid as a separate comedication for adjustment (sensitivity analysis 6) and the multiple imputation of missing urbanity level (sensitivity analysis 7). When the stroke outcome was conceptualized with a subdistributional hazards model (sensitivity analysis 5), which is the preferred method of taking into account competing risks when the aim is prediction but not causal inference, the risk of stroke during current-use of antidepressants was slightly but non-significantly increased and the risk of stroke during recent-use and past-use of antidepressants was decreased compared to the main analysis.

When all stroke events that occurred during the initial month of antidepressant use were considered to occur before the dispensation rather than after (sensitivity analysis 2), the direction of the effect of antidepressant current-use on the composite outcome changed direction and the risk became slightly decreased compared to no antidepressant use, but the current-use of antidepressants still posed harm with regard to the stroke event. The pattern of decreased death during current-use and increased death following discontinuation of antidepressants may be attributable to the limitation of our data source of dispensation to outpatients because the odds of being hospitalized within current-use was more likely than being hospitalized during other time periods (sensitivity analysis 3). Also, two drug classes tested other than antidepressants, nonsteroidal anti-inflammatory drugs and antipsychotics, showed a similar trend in terms of trend of death, in support of the above-mentioned hypothesis (sensitivity analysis 4). All statistics from the main unadjusted and fully adjusted analyses, sensitivity analyses and analysis for effect modification by sex are available in Appendix S1.

DISCUSSION

The risk of stroke or death was significantly higher during antidepressant use than with no antidepressant use. The use of antidepressants other than TCAs or SSRIs increased the risk of stroke or death. Also, previous use of antidepressants from multiple classes highly increased this risk. Amongst antidepressant classes, the hazard of death or stroke was the lowest with TCA use. Risk of antidepressant-related stroke was highest whilst on treatment and gradually decreased but stayed significantly high up to 12 months following discontinuation. Risk of antidepressant-related death was significantly lower than no antidepressant use during treatment but significantly increased after withdrawal.

TABLE 2 Risk of antidepressant use compared to no antidepressant use

	No use	Current-use			Recent-use			Past-use		
	n	HR (95% CI)	*p* value	*n*	HR (95% CI)	*p* value	*n*	HR (95% CI)	*p* value	*n*
Composite outcome	168,922	1.04 (1.02–1.06)	<0.0001	15,755	3.34 (3.27–3.41)	<0.0001	9165	2.06 (2.02–2.10)	<0.0001	10,439
Death	146,954	0.93 (0.91–0.94)	<0.0001	13,183	3.59 (3.52–3.67)	<0.0001	9441	2.17 (2.13–2.22)	<0.0001	10,430
Stroke (total)	29,400	1.56 (1.50–1.61)	<0.0001	3847	1.45 (1.33–1.58)	<0.0001	546	1.21 (1.13–1.30)	<0.0001	859
Fatal stroke	959	1.31 (1.09–1.59)	<0.01	138	1.63 (1.10–2.43)	0.02	26	1.03 (0.70–1.50)	0.89	28
Ischaemic stroke	4879	1.65 (1.51–1.80)	<0.0001	665	1.36 (1.10–1.69)	<0.01	84	1.00 (0.83–1.20)	1.00	118
Hemorrhagic stroke	2170	1.73 (1.53–1.96)	<0.0001	312	2.27 (1.76–2.94)	<0.0001	62	1.32 (1.04–1.69)	0.02	69
Unspecified stroke	22,337	1.52 (1.46–1.58)	<0.0001	2868	1.39 (1.26–1.54)	<0.0001	400	1.25 (1.15–1.35)	<0.0001	672

Note: Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs), and number of outcome events (*n*) for episodes, including the reference category of no antidepressant use.

FIGURE 2 Risk of antidepressant use compared to no antidepressant use by antidepressant class—composite outcome. Summary graphics of hazard ratios (with 95% confidence intervals) of use episodes to no antidepressant use by antidepressant class. SSRI, selective serotonin reuptake inhibitors; TCA, tricyclics; Others, other antidepressants; Multiple, more than one class of antidepressant in a single use episode

FIGURE 3 Risk of antidepressant use compared to no antidepressant use by antidepressant class—outcome death. Summary graphics of hazard ratios (with 95% confidence intervals) of use episodes to no antidepressant use by antidepressant class. SSRI, selective serotonin reuptake inhibitors; TCA, tricyclics; Others, other antidepressants; Multiple, more than one class of antidepressants in a single use episode

In a database of outpatients being reimbursed, antidepressant use was associated with significantly lower mortality compared to no antidepressant use in individuals aged over 10 [13]. Prospective studies in elderly cohorts found no such decrease in risk [11,12]. In our study, compared to those who were not using antidepressants, 10% fewer deaths were observed amongst patients using antidepressants. However, following treatment discontinuation, 3.6 times more patients died during the initial 2 months and 2.2 times more

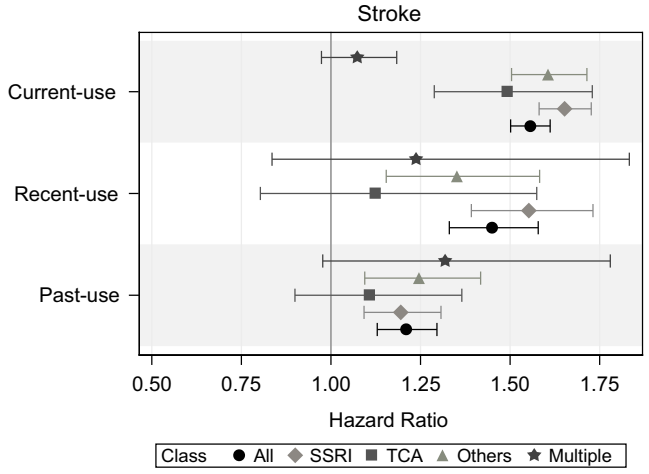

FIGURE 4 Risk of antidepressant use compared to no antidepressant use by antidepressant class—outcome stroke. Summary graphics of hazard ratios (with 95% confidence intervals) of use episodes to no antidepressant use by antidepressant class. SSRI, selective serotonin reuptake inhibitors; TCA, tricyclics; Others, other antidepressants; Multiple, more than one class of antidepressants in a single use episode

patients died during the following period up to 12 months. Drug reimbursement information was only available from outpatients, which might have caused misclassification of exposure. Persons with worsening health are likely to be hospitalized. This might have caused informative stopping of reimbursement and create an artificial risk increase afterwards. This unexpected finding might also be explained by the tendency of the elderly to be deprescribed the drugs for less critical indications like mental health problems when they are close to death [19]. Or, elderly individuals with health problems requiring antidepressant treatment would be at increased risk of death after discontinuing antidepressants.

Based on a total of 10 observational studies, a meta-analysis concluded that, compared to no antidepressant treatment, SSRI use significantly increased cerebrovascular disease risk, whilst TCAs did not [20]. This result was confirmed by a later study in an elderly Italian cohort with existing cardiovascular diseases [21]. In our study, controlling for history of cardiovascular diseases, a higher stroke risk associated with the use of all antidepressant classes was found, except for current simultaneous use of multiple antidepressant classes. Similarly, a case-crossover study found increased stroke risk with all antidepressants, the most pronounced being SSRIs, followed by other antidepressants, and TCAs. Yet the class differences were not significant [22], similar to a study investigating different cardiovascular event risks between SSRI and non-SSRI users [23]. Although our results indicate an increased risk of stroke with current antidepressant treatment, any conclusion should be treated with caution. One-third of stroke events occurred during the initial month of antidepressant reimbursement and may have been misclassified as an event because only the month of exposure, not the exact date, was available to us. Either antidepressant exposure has an immediate effect on risk of stroke or post-stroke antidepressant treatment is common. The literature on prophylactic antidepressant treatment in stroke survivors makes both options probable [24].

High population coverage of our real-world data source and not restricting the indication during cohort selection make our results generalizable. Another strength of this study is its reliance on reimbursement data to determine the antidepressant exposure, considered an accurate source in pharmacoepidemiology [25]. Although medications paid out-of-pocket are absent and secondary treatment adherence is unclear in reimbursement datasets, these limitations would lead to bias towards the null and not undermine our results. Data from death registries are also considered valid. However, diagnoses of stroke may be incompletely reflected in primary care records. Still, after adjusting for health-seeking behavior, no differential recording of diagnoses within antidepressant exposure and non-exposure periods was expected.

From our analysis, it cannot be inferred by which mechanism antidepressants affect the risk of stroke or mortality. It has been suggested that increased fibrinolytic activity and weight gain may mediate the effect of antidepressants on bleeding or thrombotic events [26]. These are interesting hypotheses for future studies. Antithrombotic drugs, like serotonergic antidepressants, are known to increase the risk of bleeding. Also, atrial fibrillation is known to increase the risk of stroke. In our cohort, significantly more antidepressant users had atrial fibrillation and were on antithrombotic drugs than antidepressant never-users, although the significance of these differences is due to the high number of participants. Our analysis and reported effect estimates are adjusted for these and other possibly confounding comorbidities and comedications. The sensitivity analyses taking into account acetylsalicylic acid as a separate category of comedication and serotonergic antidepressants as a single category did not substantially change the results. Yet, another potential limitation may be due to the lack of data on testosterone use, which may have acted as a confounding factor and contributed to stroke or death, especially in men [27].

In conclusion, antidepressant use may be associated with increased risk of stroke or mortality in the elderly. These results should be treated with caution because residual confounding or misclassification cannot be ruled out. The highly increased mortality risk following the discontinuation of antidepressant treatment warrants further analysis. Prior to initiating antidepressant therapy in the elderly, physicians should evaluate its possible benefits against the possible risks of stroke or death.

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SIDIAP and the Department of Health provided the data. This article has not been written in conjunction with the professionals of the database. The results and conclusions are the sole responsibility of the authors of this study. Drs Pili Ferrer and Lina Camacho contributed to the study's conception.

CONFLICT OF INTEREST

The authors have no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Irmak B. Ön: Conceptualization (equal); data curation (equal); formal analysis (lead); methodology (equal); visualization (lead); writing—original draft (lead); writing—review and editing (equal). Xavier Vidal: Conceptualization (equal); formal analysis (supporting); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Ursula Berger: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Mònica Sabaté: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Elena Ballarín: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Olga Maisterra: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Antonio San-Jose: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting). Luisa Ibáñez: Conceptualization (equal); funding acquisition (lead); methodology (equal); supervision (equal); writing—original draft (supporting); writing—review and editing (supporting).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study belong to the Jordi Gol Institut and SIDIAP database. Restrictions apply to the availability of these data, which were used under license for this study.

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