

Research paper

## Risk of dementia among antidepressant elderly users: A population-based cohort analysis in Spain

Javier Santandreu<sup>a</sup>, Francisco Félix Caballero<sup>b</sup>, M. Pilar Gómez-Serranillos<sup>a</sup>, Elena González-Burgos<sup>a,\*</sup>

<sup>a</sup> Department of Pharmacology, Pharmacognosy and Botany, Faculty of Pharmacy, Universidad Complutense de Madrid, Madrid, Spain

<sup>b</sup> Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid and CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain



## ARTICLE INFO

## Keywords:

Antidepressants  
Dementia  
BIFAP  
Cohort study  
Anticholinergic

## ABSTRACT

The use of antidepressants with anticholinergic effects has been associated with an increased risk of dementia. However, the results published are contradictory. The aim of the study is to compare the risk of developing dementia in elderly who were prescribed tricyclic antidepressants (TCA) versus those who were prescribed selective serotonin reuptake inhibitors (SSRIs) and other antidepressants (OA). A prospective population-based cohort study was performed using the Spanish Database for Pharmacoepidemiological Research in Primary Care (BIFAP) data (from 2005 to 2018). The cohort study included 62,928 patients age  $\geq 60$  without dementia and with antidepressant long-term monotherapy. Patients were divided into exposure antidepressant groups based on ATC system [TCA, SSRIs users and OAs users]. The risk of dementia was calculated by Cox regression models, providing hazard ratios (HR) and 95 % confidence intervals. The Kaplan-Meier model was used for survival analysis. Chi2 test was used as association test. The results showed SSRI users had higher dementia risk than TCA users (HR = 1.864; 95%CI = 1.624–2.140). Moreover, OA users had also significant risk of dementia (HR = 2.103; 95%CI = 1.818–2.431). Several limitations are the variation of the trend in the prescription of antidepressants, the small number of patients that use some antidepressants, the lack of information related to the dose, or socioeconomic characteristics, the use of antidepressant drugs for other indications, or the therapeutic compliance.

Our findings showed that older users of SSRI and OA have more risk of developing dementia than TCA elderly users. However, additional studies would be needed.

### 1. Introduction

Dementia is a chronic and progressive syndrome that affects cognitive function and behavior (i.e., memory loss, agnosia, apraxia, language impairments) leading to patient disability and mortality, and with a great economic and emotional impact for the family and the health system (Duong et al., 2017; Villarejo Galende et al., 2021). Dementia affects over 55 million people worldwide. The risk of dementia increases exponentially in people over 60 years of age (World Alzheimer Report, 2021). Spain will be one of the oldest countries in the world in 2050 and it is estimated that dementia will affect nearly one million of its population (Villarejo Galende et al., 2021; Barry et al., 2014). Therefore, addressing dementia is a public health priority (World Health Organization, 2013).

Depression is a common mental disorder that suffer around 5.7 % of people older than 60 years (Evans-Lacko et al., 2018). In Spain, the prevalence of depression diagnoses is higher in women than in men (9.2 % versus 4.0 %). Moreover, women are the group with the highest prescription and consumption of antidepressants (7.9 % female versus 3.2 % male) (Ministerio de Sanidad, Consumo y Bienestar Social, 2017). Antidepressants drugs are used for the treatment of depression, but some antidepressants are also used to treat people with other mental and physical conditions such as panic disorder, obsessive compulsive disorder (OCD), attention deficit-hyperactive disorder, bulimia, or some types of pain (Sabella, 2018). In Spain, there has been an increase of 200 % in the use of antidepressants from 2000 until 2013, being selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and the group of “other antidepressants” (ATC code N06AX) the most used (Agencia

\* Corresponding author.

E-mail address: [elenagon@ucm.es](mailto:elenagon@ucm.es) (E. González-Burgos).

<https://doi.org/10.1016/j.jad.2024.01.002>

Received 26 July 2023; Received in revised form 21 November 2023; Accepted 3 January 2024

Available online 7 January 2024

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Española del Medicamento y Productos Sanitarios, 2015). Antidepressants may be associated with a neuroprotective effect or with a cognitive impairment or dementia (Goveas et al., 2012; Kessing et al., 2011; Wang et al., 2016). The neuroprotective effect is based on its anti-inflammatory and hippocampal neurogenesis properties (Dranovsky and Hen, 2006; Hashioka et al., 2009; Hwang et al., 2008), whereas the increased risk for dementia is based on its anticholinergic properties (Jessen et al., 2010). The evidence is controversial and very limited for the use of long-term treatment with antidepressant in older people with intact cognitive functions (Goveas et al., 2012; Wang et al., 2016). Therefore, identifying antidepressant treatments that may increase the risk of dementia in older people is crucial to establish therapeutic strategies more adapted to this population group.

The aim of the current study was to investigate the incidence of dementia among elderly patients exposed to different antidepressant classes using the Spanish Database for Pharmacoepidemiological Research in Primary Care (BIFAP). This is the first study carried out in Spain and supports the need detected in other studies to confirm the potential risk of dementia due to the use of certain antidepressants in other populations (Wang et al., 2016).

## 2. Methods

### 2.1. Data source

This study was performed using data from the Spanish Database for Pharmacoepidemiological Research in Primary Care (BIFAP). BIFAP is a longitudinal and dynamic population-based database of anonymized electronic health records from primary care practitioners (6419) and pediatricians (1147) from ten different Spanish regions. BIFAP is financed and administered by the Spanish Agency for Medicines and Medical Devices (AEMPS) from the Ministry of Health, Consumer Affairs and Social Welfare. This database is registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). BIFAP includes information on demographics, lifestyle factors, diagnoses, vaccinations, and drug prescriptions of >11 million patients (17.3 % of total Spanish population). The results, discussion, and conclusions of this work are only of the authors and do not represent in any way the position of the AEMPS on this subject.

The protocol of the current study was approved by the BIFAP Scientific Committee (number 20\_2019).

### 2.2. Study design

A prospective population-based cohort study was performed using available BIFAP recorded data (from 2005 to 2018). The eligible study sample were patients aged  $\geq 60$  years with no dementia at study entry and who were prescribed for the first time with an antidepressant in monotherapy authorized and marketed in Spain. The antidepressant drug had to be prescribed at least 90 days (long-term treatment). The patients had at least 1 year of previous follow-up before the study.

Exclusions criteria to our work were patients treated with several antidepressant drugs (consecutively or simultaneously), users of antipsychotic drugs and lithium or with antecedents of substance abuse and patients with a previous diagnosis of some type of dementia, schizophrenia and/or bipolarity were also excluded. Moreover, patients diagnosed with dementia within a period  $\leq 12$  months after entering the study were also excluded. In addition, patients that used drugs for the treatment of dementia including donepezil, rivastigmine, galantamine, or memantine, before the study entry were also excluded.

The main outcome of the study was the incidence of dementia during the study. For the follow-up, it was considered the first antidepressant prescription as the start date inside the study. All the patients were followed-up since the start until developing dementia, or until the stop of follow-up. It was considered stop the follow-up situations such as patient death, end of study time, and output of the database.

The flow-chart of patient selection process is summarized in Fig. 1.

### 2.3. Treatment episodes and exposure definition

The study population was divided in five exposure cohorts based on Anatomical Therapeutic Chemical (ATC) classification system: (1) N06AA Non-selective monoamine reuptake inhibitors (tricyclic antidepressants, TCA); (2) N06AB Selective serotonin reuptake inhibitors (SSRIs); (3) N06AF Non-selective amino oxidase inhibitors (MAOI NS); (4) N06AG Monoamine Oxidase A inhibitors (MAOI A) and (5) N06AX other antidepressants.

The antidepressants authorized and marketed in Spain for each of these groups are for N06AA: imipramine (N06AA02), clomipramine (N06AA04), trimipramine (N06AA06), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), maprotiline (N06AA21); for N06AB: fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08) and escitalopram (N06AB10); for N06AG: moclobemide (N06AG02) and for N06AX: mianserin (N06AX03), trazodone (N06AX05), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22), desvenlafaxine (N06AX23), St. John's Wort (N06AX259) and vortioxetine (N06AX26).

### 2.4. Covariates

Covariates were selected based on literature review on antidepressants and dementia. Sociodemographic information included age and sex. History of smoking was also assessed. The comorbidities included in this study were acute myocardial infarction, asthma, cardiac arrhythmias, cerebrovascular event, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, epilepsy/seizures, head injury, heart failure, hemorrhage, hypercholesterolemia, hypertension, hyperthyroidism, hypothyroidism, neuralgia, obesity, Parkinson's disease and parkinsonism, psychogenic pain and neuropathic pain, and rheumatoid arthritis.

### 2.5. Outcomes

The diagnostic information for dementia was identified in the BIFAP dataset by using the International Classification on Primary Care (ICPC-2) code P70 and the International Classification of Diseases (ICD-9) codes 046, 290-292, 294, 331, and 333.

### 2.6. Statistical analysis

Absolute frequencies and percentages were provided for categorical variables, while means and standard deviations were reported for continuous ones. The patients were divided into exposure antidepressant groups based on ATC system. The first group comprised patients who were prescribed tricyclic antidepressants (TCA) (control cohort), the second group was for selective serotonin reuptake inhibitors (SSRIs) users, and the third one was composed of other antidepressants users. No patients who were prescribed neither non-selective amino oxidase inhibitors (MAOI NS) nor monoamine oxidase A inhibitors (MAOI A) have been identified during the study period.

Chi-squared test was used to determinate raw the association between age, sex, smoking habits, and chronic diseases considered, and risk of dementia. The incident risk of dementia in patients exposed to different antidepressant drugs was calculated by Cox regression models, using hazard ratios (HR) and 95 % confidence intervals. Three Cox regression models were performed using a subsequential approach. Model 1 showed the risk of dementia in the SSRI antidepressant group and in the other antidepressant group compared to the TCA group (reference group) without adjusting for any covariate. Model 2 was additionally adjusted for sex while Model 3 was also adjusted for all

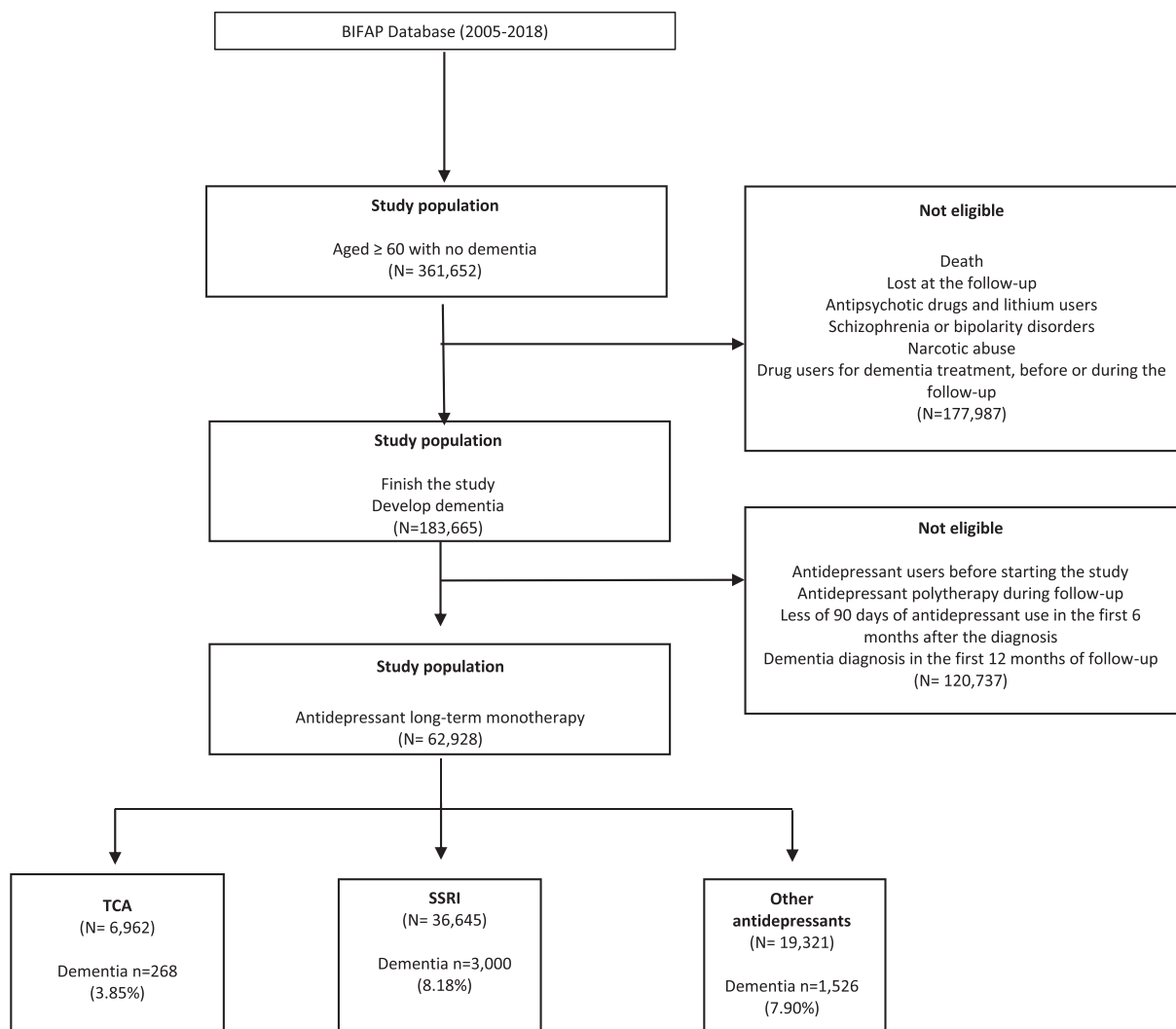


Fig. 1. Study flow chart.

listed covariates. The covariates used to adjust the Model 3 were smoking habit, acute myocardial infarction, asthma, cardiac arrhythmias, cerebrovascular event, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, epilepsy/seizures, head injury, heart failure, hemorrhage, hypercholesterolemia, hypertension, hyperthyroidism, hypothyroidism, neuralgia, obesity, Parkinson's disease and parkinsonism, psychogenic pain and neuropathic pain, and rheumatoid arthritis. The Kaplan-Meier model was used for survival analysis.

Statistical significance was set at two-tailed  $p < 0.05$ . STATA version 14 and XLSTAT were used for statistical analysis.

### 3. Results

#### 3.1. Sample characteristics

A total of 62,928 patients met all the inclusion criteria and were included in the analysis. The mean age was 64.82 (SD = 8.835) and the percentage of women and men were 63.4 % and 36.6 %, respectively. Of the eligible patients, 6962 individuals were TCA users (11.0 %) of whom 6666 were users of amitriptyline (95.75 %), and the rest of the patients, were users of the other antidepressants in the group. Of all these patients who used TCA drugs, a total of 268 individuals (3.85 %) developed dementia during the study follow-up. Regarding the SSRI cohort, it consisted of 36,645 patients (58.2 %). Of SSRI users, a total of 3000

developed dementia (8.2 %). Finally, there were 19,321 patients who were users of other antidepressants (30.7 %). A total of 1526 other antidepressant users developed dementia (7.9 %) (Table 1). Overall, significant differences in age and sex have been identified between SSRI and other antidepressant users compared to the TCA cohort. Particularly, women have a higher risk of developing dementia than men (HR = 1.101;  $p$ -value = 0,007).

The association between the different chronic conditions and risk of dementia is explored in Table 2 in the three groups of antidepressant drug users. There are significant differences ( $p$ -values < 0.05) in the three groups for cerebrovascular event, diabetes mellitus, heart failure, hypercholesterolemia, hypertension, hypothyroidism, and Parkinson's disease and parkinsonism which suggest that these conditions are risk factors for developing dementia. Moreover, there has been identified cardiac arrhythmias, head injury and obesity as risk factors for dementia in the SSRI and other antidepressants cohorts ( $p < 0.05$ ). For the coronary artery disease, hyperthyroidism, neuralgia, psychogenic pain, and neuropathic pain, and rheumatoid arthritis, no significant differences were found in any cohort group.

Association between cohorts and the risk of dementia in elderly patients.

The incidence was higher in the SSRI group (7.15 %) and in the other antidepressants group (6.0 %) compared with the TCA group (reference) (3.6 %). When adjusting for the covariates considered, SSRI users had significantly higher dementia risk than TCA users (HR = 1.792; 95 % CI

**Table 1**  
Use of antidepressants among patients included in the analysis.

TCA							
	amitriptyline	clomipramine	doxepin	imipramine	maprotiline	nortriptyline	trimipramine
N	6666	104	50	45	56	36	5
Age (mean (SD))	62.5 (8.3)	62.9 (8.3)	64.9 (8.4)	64.1 (7.5)	65.4 (8.2)	61.9 (7.6)	74.2 (11.7)
Men (%)	2457 (36.9)	37 (35.6)	24 (48)	29 (64.4)	25 (44.6)	10 (27.8)	0 (0)
Women (%)	4209 (63.1)	67 (64.4)	26 (52)	16 (35.6)	31 (55.4)	26 (72.2)	5 (100)
SSRI							
	citalopram	escitalopram	fluoxetine	fluvoxamine	paroxetine	sertraline	
N	4070	14,241	2474	118	7117	8625	
Age (mean (SD))	66.4 (8.8)	63.6 (8.8)	61.9 (8.5)	68.2 (9.0)	63.9 (8.7)	65.9 (8.7)	
Men (%)	1256 (30.9)	4922 (34.6)	807 (32.6)	43 (36.4)	2078 (29.2)	3187 (37.0)	
Women (%)	2814 (69.1)	9319 (65.4)	1667 (67.4)	75 (63.6)	5039 (70.8)	5438 (63.0)	
Other antidepressant							
	agomelatine	bupropion	desvenlafaxine	duloxetine	mianserin		
N	263	277	826	3490	321		
Age (mean (SD))	62.9 (8.8)	57.5 (7.1)	61.0 (8.6)	63.6 (8.3)	68.8 (9.0)		
Men (%)	122 (46.4)	177 (63.9)	350 (42.4)	1357 (38.9)	107 (33.3)		
Women (%)	141 (53.6)	100 (36.1)	476 (57.6)	2133 (61.1)	214 (66.7)		
Other antidepressant (continued)							
	mirtazapine	reboxetine	trazodone	venlafaxine	vortioxetine		
N	5238	9	6962	1584	351		
Age (mean (SD))	67.5 (9)	63.6 (11.0)	69.6 (9.3)	64.8 (8.8)	61.5 (8.5)		
Men (%)	2138 (40.8)	3 (33.3)	3210 (46.1)	565 (35.7)	152 (43.3)		
Women (%)	3100 (59.2)	6 (66.7)	3752 (53.9)	1019 (64.3)	199 (56.7)		

= 1.557–2.061;  $p < 0.001$ ). In addition, other antidepressant users had also significant risk for suffering of dementia (HR = 1.958; 95 % CI = 1.687–2.271;  $p$ -value < 0.001). After adjusting for gender, a higher risk was found between female patients compared to male patients (Table 3).

As shown by the Kaplan-Meier curves in Fig. 2 Kaplan-Meier survival analysis, there were differences in survival distribution among antidepressant group users. When the survival curves of the TCA group (control) and the SSRI group are compared, the graphs are similar, but the rate of dementia is higher for the SSRI users. On the other hand, the differences were much greater when we compared the Kaplan-Meier curves of the TCA group (control) and the other antidepressant group, being the development of dementia earlier and in greater numbers in users of other antidepressants.

#### 4. Discussion

This prospective population-based cohort study includes 62,928 patients aged  $\geq 60$  years with a long-term monotherapy with antidepressants and it aims to investigate the risk for dementia among antidepressant users. The antidepressants authorized and marketed in Spain used for elderly people with depression in the current work include non-selective monoamine reuptake inhibitors (TCA: amitriptyline, clomipramine, doxepin, imipramine, maprotiline, nortriptyline and trimipramine), selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and other antidepressant (agomelatine, bupropion, desvenlafaxine, duloxetine, mianserin, mirtazapine, reboxetine, trazodone, venlafaxine and vortioxetine). The clinical guides for the treatment of depression in adults recommend avoiding the TCA antidepressants in some circumstances such as seizures, epilepsy, recent myocardial infarction, and in combination with other anticholinergic drugs such as antihistaminic and antipsychotics (Grupo de trabajo de la Guía de Práctica Clínica sobre el

Manejo de la Depresión en el Adulto, 2014). Our works confirms that the main antidepressant drugs prescribed in the elderly population in Spain belong to SSRI drug group and to other antidepressants group.

Previous studies have shown that there is a higher risk of suffering from dementia in those elderly people who use antidepressant compared to those who do not take these drugs (Kodesh et al., 2019), therefore healthcare providers should prescribe antidepressants carefully (Shilyansky et al., 2016; Wang et al., 2018). However, there are very limited studies investigating which pharmacological group of antidepressants increases the risk of dementia and the results are contradictory (Kodesh et al., 2019; Then et al., 2017). These differences can be attributed to the different use of antidepressants according to countries, to the duration of the treatments and to the use of different covariates. Our initial hypothesis is that the risk of dementia will be greater in those users of antidepressants with anticholinergic properties such as tricyclic antidepressants (Then et al., 2017). Alzheimer's disease (AD) and dementia are characterized by a cholinergic deficit in various neurons. The treatment for these diseases is based on the use of acetylcholinesterase inhibitors, which increase the acetylcholine content in the synaptic cleft. There has been observed that patients with mild cognitive impairment (MCI) have the acetylcholinesterase enzyme activity decreased, but other enzymes such as choline acetyltransferase are increased its activity. This enzyme up-regulation only appears in the MCI phase (first stage of dementia). However, when the dementia progresses, the activity of this enzyme decreases. This occurs because early in the disease, the body itself attempts to stabilize acetylcholine levels in the synaptic gap (Then et al., 2017). The use of drugs with anticholinergic properties such as TCAs will accelerate cognitive impairment in patients in an early stage of MCI because body will not be able to maintain adequate levels of acetylcholine. However, our results show that the risk of developing dementia is doubled and the time to manifest the event of interest is reduced in those SSRI and other antidepressant users than in TCA users.

**Table 2**  
Association between chronic conditions and risk of dementia in different antidepressant drugs groups.

Covariates	Exposed to TCA (N = 6962)	Chi square statistic (df)/ANOVA (df)	p-value	Exposed to SSRI (N = 36,645)	Chi square statistic (df)/ANOVA (df)	p-value	Exposed to other antidepressants (N = 19,321)	Chi square statistic (df)/ANOVA(df)	p-value
Age (mean)	65.14	reference		65.20	ANOVA = 185.086 (1)	<0.001	64.13	ANOVA = 798.386 (1)	<0.001
Sex: male n, (%)	2582 (37.1)	reference		12,293 (33.5)	155.64 (1)	<0.001	8181 (42.3)	149.50	<0.001
Sex: female n, (%)	4380 (62.9)			24,352 (66.4)			11,140 (57.6)		
Smoking habit (n, %)	1389 (19.9)	1.26 (1)	0.261	7320 (19.9)	23.38 (1)	<0.001	3887 (20.1)	12.13 (1)	<0.001
Acute myocardial infarction (n, %)	163 (2.3)	0.09 (1)	0.76	1313 (3.5)	24.73 (1)	<0.001	821 (4.2)	1.16 (1)	0.281
Asthma (n, %)	463 (6.6)	0.50 (1)	0.48	2321 (6.3)	0.001 (1)	0.999	1370 (7.0)	5.82 (1)	0.016
Cardiac arrhythmias (n, %)	738 (10.6)	3.02 (1)	0.082	5163 (14.0)	32.64 (1)	<0.001	3491 (18.0)	28.70 (1)	<0.001
Cerebrovascular event (n, %)	352 (5.0)	14.62 (1)	<0.001	2619 (7.1)	73.10 (1)	<0.001	1586 (8.2)	49.96 (1)	<0.001
Chronic obstructive pulmonary disease (n, %)	419 (6.0)	3.24 (1)	0.07	2240 (6.1)	21 (1)	<0.001	1774 (9.1)	2.15 (1)	0.142
Coronary artery disease (n, %)	75 (1.0)	3.03 (1)	0.08	571 (1.56)	2.49 (1)	0.115	452 (2.3)	0.23 (1)	0.634
Diabetes mellitus (n, %)	1459 (20.9)	9.22 (1)	0.02	7333 (20.0)	57.11 (1)	<0.001	4764 (24.6)	4.89 (1)	0.027
Epilepsy/seizures (n, %)	96 (1.3)	1.52 (1)	0.22	518 (1.4)	9 (1)	0.003	334 (1.7)	1.84 (1)	0.175
Head injury (n, %)	133 (1.9)	0.16 (1)	0.69	718 (1.9)	6.27 (1)	<0.05	537 (2.7)	4.86 (1)	0.027
Heart failure (n, %)	204 (2.9)	11.42 (1)	0.001	1548 (4.2)	74.75 (1)	<0.001	1535 (7.9)	33.59 (1)	<0.001
Hemorrhage (n, %)	35 (0.5)	0.094 (1)	0.76	345 (0.9)	8.48 (1)	0.004	213 (1.1)	0.66 (1)	0.417
Hypercholesterolemia (n, %)	2436 (34.9)	10.47 (1)	<0.001	12,049 (32.8)	43.93 (1)	<0.001	6784 (35.1)	36.97 (1)	<0.001
Hypertension (n, %)	3875 (55.6)	3.94 (1)	<0.05	22,101 (60.3)	39.64 (1)	<0.001	12,607 (65.2)	9.94 (1)	0.002
Hyperthyroidism (n, %)	138 (1.9)	0.34 (1)	0.56	854 (2.3)	1.04 (1)	0.307	463 (2.4)	0.90 (1)	0.343
Hypothyroidism (n, %)	738 (10.6)	5.33 (1)	<0.05	3507 (9.5)	34.82 (1)	<0.001	1865 (9.6)	5.22 (1)	0.022
Neuralgia (n, %)	671 (9.6)	1.19 (1)	0.275	574 (1.5)	3.39 (1)	0.066	415 (2.1)	0.05 (1)	0.822
Obesity (n, %)	2450 (35.1)	0.03 (1)	0.864	12,509 (34.1)	18.86 (1)	<0.001	6836 (35.3)	23.51 (1)	<0.001
Parkinson's disease and parkinsonism (n, %)	97 (1.3)	11.09 (1)	0.001	636 (1.7)	79.04 (1)	<0.001	526 (2.7)	57.98 (1)	<0.001
Psychogenic pain and neuropathic pain (n, %)	77 (1.1)	3.12 (1)	0.077	58 (0.1)	3.23 (1)	0.072	80 (0.4)	1.9 (1)	0.168
Rheumatoid arthritis (n, %)	121 (1.7)	0.10 (1)	0.75	437 (1.1)	0.32 (1)	0.571	258 (1.3)	1.04 (1)	0.309

Particularly, the other antidepressant users need ten years for decreasing a 14 % the survival of the patients to the outcome, whereas SSRI and TCA users would need fourteen years, and more than fourteen years respectively, for reach the same result.

Although the mechanism of action of which TCA increase the risk of dementia is known, and there are several studies that confirm that their use increases the risk compared to other groups of antidepressants, the results are not clear. Hence, Kessing et al. (2011) found that monotherapy with TCA increases the risk of dementia, but only in short-term treatment (Kessing et al., 2011). When TCA treatment was a long-term monotherapy, the risk of dementia is decreased. Moreover, Then et al. (2017) found a higher risk of dementia among SSRI antidepressant users (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) than among TCA antidepressant users (amitriptyline, imipramine and doxepin) (Lee et al., 2016). However, they found that venlafaxine users had a higher risk of developing dementia than SSRI users. In another study, Lee et al. (2016) reached the same conclusion. SSRI users were in higher risk of developing dementia than TCA users and MAOI users (Schmitt et al., 2006). Moreover, this retrospective case-control study demonstrated that the risk of dementia is increased when the dose of antidepressant accumulates, being this risk greater in those SSRI users. In fact, cumulative doses of TCA showed a decreased risk of dementia (Kessing et al., 2011; Schmitt et al., 2006). Furthermore, Wang et al. (2016) determined in a retrospective cohort study that the risk of

dementia was greater in SSRIs users than in other antidepressant users and in non-users of antidepressants (Wang et al., 2016).

The biological pathway that explains the increased risk of dementia with SSRI drugs is still unclear. The first hypothesis suggests that it is due to the alteration of serotonin-regulated processes in several areas of the brain (Lee et al., 2016). Serotonin is involved in several brain functions such as mood regulation, attention, or memory (Lavrador et al., 2021). Then serotonin alteration triggers a brain metabolism decrease and accelerates the dementia progression (Wang et al., 2018). Another hypothesis is related to the zinc pathway; an excessive or low level of zinc in the brain can lead to neurofibrillary tangles. The imbalance in zinc level comes from the up-regulation of the GPR39 Zn<sup>2+</sup>-sensing receptor protein. This up-regulation has been observed in animal models after SSRI drugs administration, but not after TCA drugs administration (Wang et al., 2016).

On the other hand, the group of other antidepressants is made up of drugs with a variety of mechanisms of action. Hence, there are included antidepressants that block autoreceptor 2 and/or serotonergic receptors such as mianserin, mirtazapine and trazodone, noradrenaline and dopamine reuptake inhibitor such as bupropion, modulators of serotonin receptors such as vortioxetine, noradrenaline reuptake inhibitor such as reboxetine, modulators of some neurotransmitters such as noradrenaline or serotonin (desvenlafaxine, venlafaxine and duloxetine) and finally, agomelatine which is a melatonin receptor agonist. This

**Table 3**  
Association between cohorts and the risk of dementia in elderly patients.

Model 1. Cox regression						
Cohort	Incidence (%)	n/N	HR	(95 % CI)	p-value	
TCA	3.6	221/6104	reference	reference	reference	
SSRI	7.1	2324/32,471	1.86	(1.62–2.14)	<0.001	
Other antidepressants	6.7	1052/15,694	2.10	(1.82–2.43)	<0.001	
Model 2. Cox regression after adjusting by sex						
Cohort	I male/I female (%)	n/N male; n/N female	HR	(95 % CI)	p-value	
TCA	2.5/4.2	58/2234;163/3870				
SSRI	6.8/7.3	727/10,638;1597/21,833				
Other antidepressants	5.68/7.4	368/6475;684/9219				
Men	5.9	1153/19,347	reference	reference	reference	
Women	6.9	2444/34,922	1.10	(1.03–1.18)	0,007	
Model 3. Cox regression after adjusting by covariates						
Cohort	Incidence (%)	n/N	HR	(95 % CI)	p-value	
TCA	3.6	221/6104	reference	Reference	reference	
SSRI	7.1	2324/32,471	1.79	(1.56–2.06)	<0.001	
Other antidepressants	6.7	1052/15,694	1.96	(1.69–2.27)	<0.001	
Smoking habit	37.7	10,539/27,932	0.77	(0.70–0.84)	<0.001	
Acute myocardial infarction	3.4	1874/54,269	1.37	(1.17–1.59)	<0.001	
Asthma	6.3	3444/54,269	0.97	(0.85–1.12)	0.709	
Cardiac arrhythmias	13.9	7572/54,269	1.29	(1.18–1.42)	<0.001	
Cerebrovascular event	6.8	3719/54,269	1.54	(1.39–1.72)	<0.001	
Chronic obstructive pulmonary disease	6.6	3614/54,269	1.31	(1.16–1.48)	<0.001	
Coronary artery disease	1.6	870/54,269	1.53	(1.20–1.95)	<0.001	
Diabetes mellitus	21.0	11,400/54,269	1.31	(1.21–1.42)	<0.001	
Epilepsy/seizures	1.4	791/54,269	1.24	(0.97–1.58)	0.0897	
Head injury	1.9	1070/54,269	1.44	(1.16–1.78)	<0.001	
Heart failure	4.6	2509/54,269	1.75	(1.53–2.00)	<0.001	
Hemorrhage	0.8	472/54,269	1.53	(1.12–2.08)	0.007	
Hypercholesterolemia	33.3	18,104/54,269	0.78	(0.73–0.84)	<0.001	
Hypertension	60.7	32,944/54,269	1.30	(1.21–1.40)	<0.001	
Hyperthyroidism	2.2	1216/54,269	1.05	(0.84–1.31)	0.659	
Hypothyroidism	9.4	5126/54,269	0.83	(0.73–0.95)	0.0048	
Neuralgia	2.5	1406/54,269	0.97	(0.78–1.21)	0.788	
Obesity	34.3	18,646/54,269	0.76	(0.71–0.82)	<0.001	
Parkinson's disease and parkinsonism	1.8	990/54,269	2.38	(2.00–2.83)	<0.001	
Psychogenic pain and neuropathic pain	0.3	181/54,269	0.27	(0.09–0.82)	0.02	
Rheumatoid arthritis	1.1	648/54,269	1.09	(0.81–1.46)	0.584	

Patients were followed until the diagnosis or the end of the study time (2018). In the 3 models, patients with less of 365 days of follow-up were removed from the analysis. SSRI, selective serotonin reuptake inhibitor. TCA non-selective monoamine reuptake inhibitors. HR, hazard ratios. CI, confidence interval.

mechanistical diversity explained the higher risk of dementia in other antidepressant compared to TCA drugs users.

Anticholinergic burden is the cumulative effect of exposure to several drugs with anticholinergic effects at the same time (Heser et al., 2018). It is important to note that the anticholinergic burden of TCA antidepressants is greater than the anticholinergic burden of antidepressants with non-selective reuptake inhibitory action. Particularly, six of the seven TCA drugs included in our study are classified as potentially inappropriate medications.<sup>26</sup>

Finally, it is important to consider the large number of covariates used to fit the Cox regression model. There are several pathologies and conditions that can act as risk factors for dementia. For example, different vascular pathologies are risk factors for dementia. Other covariates that have shown risk for dementia are chronic obstructive pulmonary disease, diabetes mellitus, head injuries, and Parkinson's disease and parkinsonism.

The main strengths of our study are the length of follow-up and the total number of patients (representative of the Spanish population). However, our work has several limitations. Throughout the entire study (from 2005 to 2018), the trend in the prescription of antidepressants has varied. Some antidepressants have only been on the market for a few years (i.e. vortioxetine has been marketed in Spain from 2014), and the

number of patients who have used them is smaller, or the follow-up time in the study since their prescription is short. Moreover, other antidepressant such as tricyclic antidepressant is in disuse; amitriptyline is the most prescribed TCA drug ( $n = 6666$  of a total of 6962 patients that used TCA drugs). Furthermore, there is a lack of information related to the dose, adverse reactions, socioeconomic characteristics, or efficacy of the treatments.

The lack of information on sociodemographic characteristics and family history is due to the lack of availability of these factors in BIFAP dataset. Therefore, it may be a limitation of the study that prescribers avoid TCAs in patients at increased risk of dementia. However, patients' risk of dementia is partly controlled by adjustment in the Cox regression model for all covariates in the study, most of which act as risk factors for the development of dementia. Another limitation is that antidepressant drugs are used for different pathologies other than depression such as insomnia or kind of pain. Therefore, since depression could be a risk of factor for dementia, given that there are other indications for antidepressant drugs, depression could be a confounding factor.

However, all the antidepressant drugs of this study have the treatment of depression as the first indication of use. Therefore, it is expected that most patients of this study, who have been using antidepressants for several years and in long-term treatments, would be for the treatment of

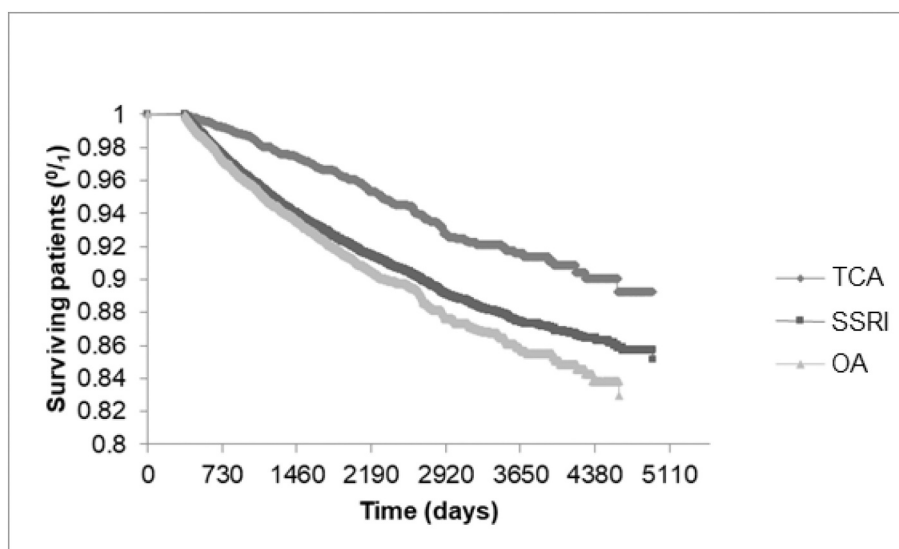


Fig. 2. Kaplan-Meier survival curve. TCA: non-selective monoamine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors and OA: other antidepressants users.

depression. Moreover, some antidepressants such as doxepin or nortriptyline (both of which are TCAs), are only indicated for the treatment of depression and depressive symptoms. These facts, together with the large number of patients, the duration of follow-up and the subsequential approach used to perform the three Cox regression models help to control the indication bias mentioned above.

The third limitation is related to therapeutic compliance, since in the study we consider that all patients adequately take the prescribed medication. On the other hand, it is well known that dementia is underdiagnosed, so it could be that patients not diagnosed with dementia could have cognitive decline. Finally, the number of women is different in each antidepressant group; since sex could be a risk factor, risk of dementia could be overestimated.

## 5. Conclusion

In conclusion, our findings showed that SSRI and other antidepressants elderly users have more risk of developing dementia than TCA elderly users. However, these data are not definitive for the elderly population, requiring more studies to implement the most appropriate therapeutic strategies for this group.

## Funding information

Authors state no funding involved.

## CRediT authorship contribution statement

**Javier Santandreu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Francisco Félix Caballero:** Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing, Conceptualization, Data curation, Writing – original draft. **M. Pilar Gómez-Serranillos:** Supervision, Visualization, Writing – review & editing. **Elena González-Burgos:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The corresponding author Elena González-Burgos, on behalf of all

authors listed in the paper “Risk of dementia among antidepressant elderly users: a population-based cohort analysis in Spain” certify that there is no actual or potential of interest in relation to this article.

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