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Antidepressant use in the elderly is associated with an increased risk of dementia

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Abstract

A retrospective cohort study was conducted including 3,688 patients age 60 years or older without dementia enrolled in a depression screening study in primary care clinics. Information on antidepressant use and incident dementia during follow-up was retrieved from electronic medical records. Cox's proportional hazard models were used to compare the risk for incident dementia among five participant groups: SSRI only, non-SSRI only (Non-SSRI), mixed group of SSRI and non-SSRI, not on antidepressants but depressed, and not on antidepressants and not depressed. SSRI and Non-SSRI users had significantly higher dementia risk than the non-depressed non-users (HR=1.83, p=0.0025 for SSRI users and HR=1.50, p=0.004 for non-SSRI users). In addition, SSRIs users had significantly higher dementia risk than non-users with severe depression (HR=2.26, p=0.0005).

Future research is needed to confirm our results in other populations and to explore potential mechanism underlying the observed association.

Keywords

Antidepressants; Dementia; Retrospective cohort study

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The authors report no conflicts of interest. Chenkun Wang and Sujuan Gao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

1. Introduction

Depression is common among elderly patients with prevalence rates around 10–15% for those living in the community[1–3]. Antidepressants are one of the most commonly prescribed drugs in the United States. In the 1990s, selective serotonin re-uptake inhibitors (SSRI) became the first line of drug treatment for depression, replacing tricyclic antidepressants (TCA)[4]. Antidepressants have been hypothesized to have neuroprotective effects[5,6] such as improved memory and cognition[7]. In addition, it has been suggested that treatment with SSRIs may improve cognitive function in patients with Alzheimer's dementia[8], although this is not consistent across studies. However, little is known about the long-term outcomes of antidepressant use in the elderly population with intact cognitive functions. Older adults are often under-represented in clinical trials of antidepressants and the short duration of such trials are often limited to a few weeks or months[9,10]. There have been few long-term studies to date investigating the association between antidepressant use and the risk of dementia.

Prior reports have pointed to potentially differential and complex relationships between different types of antidepressants and dementia risk[11,12]. A nationwide study in Denmark found that the rate of developing dementia was higher among persons exposed to antidepressants compared to those unexposed to antidepressants[11]. However, in a follow-up study, the authors reported that continued long-term treatment with older antidepressants, such as TCAs, was associated with a reduced rate of dementia, whereas continued treatment with other classes of antidepressants including SSRIs was not[13]. A cohort study of postmenopausal women aged 65 to 79 years reported that antidepressant use at baseline and depression severity were associated with subsequent cognitive impairment[12].

In this study, we explore the association between antidepressant use and the incidence of dementia, using data from a longitudinal observational cohort study of elderly primary care patients.

2. Method

2.1.Study population

From 1991 to 1993, all patients 60 years and older attending the primary care practice in the Wishard Health System were approached for participation in a depression screening study. A total of 4,413 primary care patients were approached, of whom 115 refused; 57 were not able to complete the testing due to severe cognitive impairment; 284 patients were not eligible because they did not speak English, were in prison or a nursing home, or had a hearing impairment, leaving 3,957 total enrolled patients. The methods and results of the depression screening program have been previously reported[14,15]. Patients who were diagnosed with dementia prior to enrollment were excluded from this analysis, resulting in a total of 3,688 patients. The study was approved by the Institutional Review Boards of Indiana University-Purdue University of Indianapolis.

2.2.Data Source

Medical history information from enrollment to December 31, 2010 was extracted from the Regenstrief Medical Record System (RMRS)[16]. For this study, we retrieved dates for

patients' first diagnoses (as indicated by the *International Classification of Diseases, Ninth Revision* (ICD-9) codes) contained in inpatient, outpatient and emergency room records for the following conditions: anemia (280 – 285), arthritis (714.,715.), atherosclerotic vascular disease (440.), cancer (140. –172. and 174. – 239.), cerebrovascular disease (CVD) (430. – 438.), congestive heart failure (CHF) (428., 398.91), coronary artery disease (CAD) (410., 411., 412., 414.), chronic obstructive pulmonary disease (COPD) (491., 492., 496.), dementia (290.0–290.43, 291.2, 294.0–294.9, 331.0–331.9, 333.0, and 797), depression (296.2, 296.3, 300.4, 309.0, 309.1, 298.0, 311), diabetes (250.), hyperlipidemia, hypertension(401.), liver disease(570. –573.), renal disease (585.), peripheral artery disease (PAD) (440.2, 443.9) and thyroid disease (242., 244.) (including both hyperthyroidism and hypothyroidism). Demographic information including age, gender, race, years of education and history of smoking were collected at study enrollment. Center for Epidemiologic Studies Depression (CESD) score for depression and a short portable mental status questionnaire (SPMSQ) value for cognitive function were also collected at enrollment.

2.3.Antidepressant Use

Medication dispensing data were retrieved from the electronic medical records for any antidepressant dispensed including medication name, dispensing date, duration and dose from enrollment through December 31, 2010 or the patient's last encounter with the health care system.

2.4. Study Endpoint

To avoid an immortal time bias[17] due to differences in the timing of antidepressant use, each subject's baseline was defined as the first date a patient was prescribed an antidepressant for those in the medication group. Baseline was defined as the date at enrollment for patients who were never prescribed antidepressants. Incident dementia was identified as the first date that each subject was assigned a new dementia diagnosis based on ICD-9 codes. Study endpoint was defined as the time of diagnosis for patients with incident dementia, and the time of the last outpatient primary care physician (PCP) visit during follow-up for patients who were not diagnosed with dementia.

3. Statistical Analysis

To examine potential differential effects of SSRI and other antidepressants and also control for the effect of depression, we divided patients into five mutually exclusive groups. The first group consisted of patients who were prescribed only SSRIs throughout the follow-up period (Group 1: SSRIs group). The second group consisted of participants who were prescribed only non-SSRI antidepressants throughout the follow-up period (Group 2: non-SSRIs group). The third group consisted of participants who were prescribed both SSRIs as well as other types of antidepressants during follow-up (Group 3: mixed group). The fourth group included participants who were not prescribed any antidepressant during follow-up but whose CESD scores at enrollment were greater than or equal to 16 or who had been diagnosed with depression prior to enrollment (Group 4: non-users with depression). The fifth group consisted of participants who were not prescribed antidepressants and had no

significant symptoms of depression at enrollment (CESD score <16 at enrollment) (Group 5: non-users no depression).

Comparison of demographic characteristics and medical history among the five groups of participants were conducted using Chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Cox proportional hazards models were used to examine whether antidepressant use was associated with dementia risk. Proportional hazard assumption was tested by including an interaction term with group indicator and time as time-dependent covariate in the Cox model. Covariates such as age or comorbid conditions were adjusted at individual baseline with the exception of CESD and SPMSQ which were measured at enrollment. Backward model selection was used to identify potential covariates in the Cox's models. Since the baseline time of patients on antidepressants was after enrollment time, the two non-user groups had longer follow-up time than the three antidepressant groups. To detect the influence from the differences in follow-up times, we conducted three sets of Cox models using three different censoring times in our analyses based on the quartile survival times (50%, 75% and 100%) in the participants on antidepressants. The first set of models used 5-year follow-up as the censoring time which was the median survival time in the three antidepressants groups. The second set of models used 9-year censoring time and the third set of models used the entire 18 years as the follow-up length.

We also conducted a sensitivity analysis by increasing the threshold of CESD score from 16 to 24 in Group 4 to compare dementia risk between severely depressed non-antidepressant participants and antidepressant users. In a second sensitivity analysis, we included medication possession ratio (MPR, defined as duration on medication divided by total time) for patients in the antidepressants groups in order to detect a dose-response relationship. SAS 9.3 was used for all analyses.

4. Results

A total of 3,688 patients were included in the analysis. Mean age at enrollment was 67.9 years (SD=7.3), with 69.1% being women. There were 14.86% patients with CESD score greater or equal to 16 and 5.04% with SPMSQ value greater than 4 indicating cognitive impairment. Median follow-up from baseline to study endpoint was 5.1 years in the cohort. A total of 574 (15%) participants were diagnosed with incident dementia during the entire observation period, of whom 231 patients were diagnosed with incident dementia during the first 5-year observation period, and 373 dementia events were identified during the first 9 years of observation period.

In Table 1, we included comparisons of demographic information and medical history at enrollment among the five patient groups. Years from enrollment to antidepressant use, number of dispensing and years on antidepressants for Groups 1, 2 and 3 were also included. While there were many differences among the five groups, the three antidepressant user groups and the non-user but depressed group differed in proportions of women, African American participants, smokers, mean years of education, mean body mass index, and history of arthritis, COPD, hypertension. These four depressed groups also differed

significantly on mean age, mean CESD score and cognitive scores. However, the SSRIs group (Group 1) and the non-SSRI group (Group 2) were similar in CESD and SPMSQ scores. The mixed group had higher rate of diagnosed depression at enrollment as well as longer antidepressant use and greater number of antidepressant dispensing when compared to the SSRI and non-SSRI groups (Table 1).

Table 2 included results from Cox's models with three different censoring times. In all three sets of models, participants who were on SSRIs (Group 1) or non-SSRIs (Group 2) during follow-up period had higher dementia risk than the depressed non-users (Group 4). No significant differences were found between mixed antidepressant users and non-users who were not depressed or between depressed non-users and not-depressed non-users.

When we increased the requirement for depression severity from CESD of 16 or higher to 24 or higher in group 4, and compared each of the antidepressant user groups to the non-users with severe depression (Table 3), we found again that SSRI users had significantly higher dementia risk than non-users with severe depression in all three sets of models with varying follow-up length (HR=2.21, p=0.01 in model 1; HR=2.19, p=0.003 in model 2; HR=2.26, p=0.001 in model 3). In addition, the difference between participants in the non-SSRI group and the severely depressed non-users was marginally significant in the 9-year follow-up model (HR=1.54, p=0.05) and became significant in the 18-year follow-up model (HR=1.62, p=0.02). In sensitivity analysis of adjusting for medication possession ratio (MPR) in the antidepressant groups, we found that both SSRIs and non-SSRI groups had significantly higher dementia risk than the mixed group (5-year model HR=2.653, p=0.0053 for the SSRIs group; HR=2.619, p=0.0017 for the non-SSRIs group). In addition, higher MPR was associated with higher dementia risk (HR=1.418 per 0.1 unit increase in MPR, p<. 0001) indicating a dose response relationship with dementia risk. Similar results were observed in the 9-year or 18-year follow-up model. We also conducted an additional sensitivity analysis by excluding participants with SPMSQ greater than 4 (indicating potential cognitive impairment) and obtained similar results.

5. Discussion

In this elderly primary care patient cohort, we found that SSRIs users were at significantly higher risk for incident dementia when compared to not depressed non-users and also when compared to non-users with depression. Patients who were taking non-SSRIs also showed significantly higher risk for incident dementia when compared to non-users without depression. Patients who took both SSRIs and non-SSRIs or who were depressed but not taking antidepressants showed no difference in dementia risk compared with non-users who were not depressed.

Few studies to date have investigated the association between antidepressant use and incidence of dementia. These studies report varying results depending on the types of antidepressants, length of treatment and the comparison group. One Danish study showed that the rate of dementia decreased during periods of two or more prescriptions of older antidepressants compared with only one prescription of older antidepressants[13]. In contrast, continued use of SSRIs or newer nonselective serotonin reuptake inhibitors was not

associated with decreased rate of dementia regardless of the subtype of dementia. Another analysis by the same group showed that people who purchased antidepressants once had an increased rate of dementia compared to persons unexposed to antidepressants[11]. A cohort study of postmenopausal women aged 65 to 79 years reported that antidepressant use at baseline, for both SSRI and TCA, and depression severity were associated with subsequent cognitive impairment when compared to non-depressed non-users[12]. When antidepressant users were compared to depressed non-users, the difference in risk for cognitive impairment was no longer significant.

One of the challenges in studying long-term outcomes in antidepressant users is untangling the effect of the medication from the potential effect of depression, the underlying condition for treatment. Previous studies have shown that late-life depression is associated with an increased risk for dementia, vascular dementia and Alzheimer's disease[18]. Hence any comparisons of antidepressant users to non-depressed non-users are subject to indication bias as the increased dementia risk could be due to depression, not the medication. As randomized trial of sufficient length comparing antidepressants to non-pharmacological interventions in depressed and non-depressed participants is likely to pose both design difficulties and raise ethical considerations, analysis of large observational cohort data may be the only way to address this question. In our analyses, by creating different groups of antidepressant users and dividing the non-users into those with depression and another group without depression, we are able to separate the potential effects due to medication use and those due to both depression and antidepressant use.

It has been hypothesized previously that antidepressants may be protective of dementia. A recent study in 23 young healthy volunteers age 18 to 50 showed that the accumulation of amyloid-β (A^2) in cerebrospinal fluid was slowed by 37% within hours with the treatment of citalopram (a SSRI) compared to placebo[19]. Other studies argued that antidepressants may have neuroprotective abilities by increasing the proliferation of neural progenitors in the hippocampus and prolonging the survival of these newborn neurons[5,6] thus leading to improved cognition[7]. Some studies have reported the association between antidepressant use and increased hippocampus volume in non-geriatric subjects[20–22]. However, other neuroimaging studies have reported that antidepressant use was significantly associated with smaller hippocampus volume[23]. A recent population-based study of older adults without dementia showed that antidepressants use was significantly associated with smaller total brain, smaller hippocampal, and larger white matter hyperintensity (WMH) volume, while high CES-D scores were not significantly associated with any of the brain measures[24]. A common limitation of these imaging studies is that they were cross-sectional in nature, and most were conducted in younger participants, thus making it difficult to infer whether the observed association was due to prolonged depression or antidepressant use.

Other studies actually suggest that antidepressant therapy may worsen the course of cognitive decline in certain patients. A recent study demonstrated that treatment of behavioral symptoms in patients with AD with SSRI antidepressants resulted in improved scores on agitation rating, but worsened scores on cognitive functions[25]. Similarly, another recent study suggested that antidepressants use in patients with early stages of AD and Lewy body dementia (LBD) worsened cortical thinning, especially the parahippocampal regions[26].

Thus, while much of the neurogenesis studies with antidepressants were seen in younger depressed subjects, quite different mechanisms may be at play in the elderly, especially those who are already in the prodromal stage of dementia.

The potential biological mechanism underlying the higher dementia risk in SSRI users is not yet clear. One animal study has demonstrated up-regulation of the GPR39 Zn^{2+}-sensing receptor protein level after SSRI treatment, but not with TCA[27]. As it has been proposed that either low Zinc or excessive Zinc may lead to neurofibrillary tangles, a primary mark of Alzheimer's disease and cognitive impairment[28,29], a potential link between SSRI use and dementia may be through the zinc pathway.

A somewhat surprising finding in our results was that patients in the mixed group were not at increased risk of dementia despite of showing higher depression diagnosis rate, longer time on antidepressants and greater number of dispensing than the SSRI and non-SSRI groups. The use of antidepressant combination is a popular strategy in practice to treat those patients with treatment resistant depression[30]. Hence it is possible that patients in the mixed group were resistant to antidepressant treatment and perhaps also immune to other deleterious brain effects of antidepressants.

Our study has a number of strength. The cohort is relatively large with long follow-up period. The use of electronic medical records (EMR) eliminates recall and potential attrition bias. A comprehensive list of medical conditions was available from EMR so that relevant covariates can be included in the analysis.

Our findings may be subject to biases and artifacts that are inherent to most observational studies. For example, one possible explanation for the observed results may be reverse causation, *i.e.* doctors either consciously or unconsciously were more likely to prescribe SSRIs rather than TCA's to older adults with cognitive impairment as there is a wide-spread recognition that TCAs have higher anticholinergic adverse effects[31,32] and if prescribers were attempting to avoid these effects, they may differentially prescribe SSRIs to older adults with cognitive impairment. A previous study has shown that depressed patients with mild cognitive impairment (MCI) were more likely to develop dementia[33]. Although we excluded patients with dementia at baseline and conducted a sensitivity analysis excluding patients with SPMSQ scores greater than 4, it is possible that participants with non-dementia cognitive impairment were still included in our analysis and the co-existence of depression with MCI may account for the higher dementia risk. However, since we also found that the SSRI group had a higher dementia risk compared to the non-users with severe depression, the inclusion of potential MCI subjects in the analyses is unlikely to account for the results.

Another potential issue in our result is ascertainment bias, *i.e.* persons with depression may be more likely to receive an early diagnosis of dementia. However, two sub-groups of patients with depression, *i.e.* those who received mixed types of antidepressants or those not receiving antidepressants, were found not at higher risk of dementia, making the ascertainment bias an unlikely explanation for our results. Providers could have also mistakenly diagnosed early cognitive impairment as depression.

The validity of using ICD-9 codes for dementia diagnosis using both inpatient and outpatient records was found to be high with sensitivity of 85.5 and specificity of 85.9[34,35]. In our study, we used ICD-9codes contained in inpatient, outpatient and emergency room records. The definition for other comorbid conditions using ICD-9 codes has been used before by various studies with established validity[36–38].

One difference in our study from previous studies is that a significant number of our subjects were African Americans. There are racial differences in response to antidepressant regimen, with African Americans generally showing significantly lower response rates than Caucasians[39]. Furthermore, depression in the elderly, especially in African Americans, is often associated with cerebrovascular disease which is also a major risk factor for cognitive decline and dementia[40].

Our study also has a number of other limitations. The medical records did not include depression severity measures after study enrollment. Hence it is not possible for us to determine whether the higher dementia risk in SSRI users was due to the lack of depression control. Similarly, no uniform dementia severity was available in the medical record system to adjust for dementia severity. In addition, we do not have information on antidepressant use prior to participant's enrollment. Thus it is not possible for us to separate the typical depression patients from patients with late-life depression. Another limitation is the use of dispensing data as a measure of medication exposure, which assumes that subjects consumed medication as prescribed. In addition, no information on the treatment indication for antidepressant use was available. Hence it is possible that some antidepressants dispensed were dispensed for non-depression indications such as pain control.

In summary, we found that SSRIs users in this elderly primary care cohort followed over 18 years were at significantly higher risk for incident dementia when compared to not depressed non-users and also when compared to non-users with depression. Given the potential for various confounding and the limited data on depression and cognitive measures, our results should be considered hypothesis generating. It will be important to see whether our results are confirmed in other studies with more detailed information on depression and cognitive function. Future studies are also needed to identify potential mechanism underlying the observed association between SSRI use and dementia risk in the elderly population.

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Table 1

Participants' characteristics at enrollment in five groups defined by antidepressant use and depression status.

Characteristics	Group 1: SSRIs (n =156)	Group 2: Non-SSRIs (n =403)	Group3: Mixed Group (n=272)	Group4: Depressed Non-user (n=548)	Group5: Non-User (CESD<16) (n=2309)	p-value*	p-value†
Age, mean (SD), year	67.1 (6.4)	66.7 (6.2)	65.8 (5.7)	67.3 (7.5)	68.5 (7.6)	**0.02**	**<.001**
Female (%)	131 (84.0)	311 (77.2)	234 (86.0)	417 (76.1)	1454 (63.0)	**0.003**	**<.001**
African American (%)	108 (69.2)	281 (69.7)	151 (55.5)	262 (47.8)	1520 (65.8)	**<.001**	**<.001**
Smoking (%)	49 (31.4)	166 (41.2)	93 (34.2)	185 (33.8)	620 (26.9)	0.05	**<.001**
Education, mean (SD)	9.1 (3.0)	8.7 (3.0)	9.2 (2.8)	8.7 (3.1)	9.0 (3.3)	0.05	**0.04**
Body mass index, mean (SD), kg/m^2	30.8 (7.0)	30.2 (7.7)	31.5 (7.6)	29.2 (8.0)	28.7 (7.2)	**<.001**	**<.001**
CESD, mean (SD)	9.5 (7.7)	9.1 (8.37)	13.8 (10.8)	19.1 (10.5)	5.1 (4.2)	**<.001**	**<.001**
SPMSQ, mean (SD)	1.4 (1.3)	1.4 (1.3)	1.1 (1.0)	1.4 (1.6)	1.5 (1.7)	**0.006**	**<.001**
History of							
Anemia (%)	34 (21.8)	96 (23.8)	52 (19.1)	102 (18.6)	402 (17.4)	0.22	**0.03**
Arthritis (%)	61 (39.1)	192 (47.6)	121 (44.5)	171 (31.2)	535 (23.2)	**<.001**	**<.001**
Atherosclerotic vascular disease (%)	4 (2.6)	7 (1.7)	2 (0.7)	13 (2.4)	40 (1.7)	0.38	0.50
Coronary artery disease (%)	39 (25.0)	100 (24.8)	67 (24.6)	158 (28.8)	428 (18.5)	0.43	**<.001**
Cancer (%)	27 (17.3)	57 (14.1)	37 (13.6)	84 (15.3)	285 (12.3)	0.72	0.18
Cerebrovascular disease (%)	16 (10.3)	45 (11.2)	23 (8.5)	63 (11.5)	230 (10.0)	0.59	0.65
Congestive heart failure (%)	30 (19.2)	72 (17.9)	46 (16.9)	122 (22.3)	346 (15.0)	0.21	**0.001**
COPD (%)	28 (18.0)	65 (16.1)	40 (14.7)	129 (23.5)	356 (15.4)	**0.005**	**<.001**
Diabetes (%)	48 (30.8)	118 (29.3)	87 (32.0)	154 (28.1)	537 (23.3)	0.69	**<.001**
Hypertension (%)	127 (81.4)	309 (76.7)	219 (80.5)	369 (67.3)	1607 (69.6)	**<.001**	**<.001**
Liver disease (%)	5 (3.2)	22 (5.5)	18 (6.6)	28 (5.1)	74 (3.2)	0.50	**0.01**
Hyperlipidemia (%)	9(5.8)	23(5.7)	6(2.2)	25(4.6)	74(3.2)	0.16	**0.03**
Renal disease (%)	1 (0.6)	0 (0)	1 (0.4)	3 (0.6)	16 (0.7)	0.51	0.53
Thyroid disease (%)	16 (10.3)	54 (13.4)	35 (12.9)	65 (11.9)	162 (7.0)	0.75	**<.001**
Depression (%)	27(17.3)	83(20.6)	84(30.9)	227(41.4)	0(0.0)	**0.001**	**<.001**
From enrollment to antidepressant use, mean(SD), year	7.1 (3.7)	5.2 (4.0)	4.4 (3.2)	NA	NA	**<.001**	NA

Characteristics	Group 1: SSRIs (n =156)	Group 2: Non-SSRIs (n =403)	Group3: Mixed Group (n=272)	Group4: Depressed Non-user (n=548)	Group5: Non-User (CESD<16) (n=2309)	p-value*	p-value†
Number of dispensing, mean(SD)	9.2 (12.4)	10.4 (15.8)	32.1 (34.6)	NA	NA	**<.001**	NA
Time on medication, mean(SD), year	1.0 (1.4)	1.1 (1.7)	3.0 (2.9)	NA	NA	**<.001**	NA

*: Comparing among Group 1 to Group 4;

†: Comparing among Group1 to Group 5;

Table 2

Cox's PH models of time to incident dementia comparing antidepressant users with non-depressed non-antidepressant participants.

	Model 1 (5-year follow-up)		Model 2 (9-year follow-up)		Model 3 (18 year follow-up)	
Parameter*, †	**Hazard Ratio**	**P-value**	**Hazard Ratio**	**P-value**	**Hazard Ratio**	**P-value**
Group 1:SSRIs	2.510	**<.001**‡	2.303	**<.001**‡	1.828	**0.003**‡
Group 2: Non-SSRIs	2.007	**<.001**‡	1.873	**<.001**‡	1.502	**0.004**‡
Group 3: Mixed Group	1.142	0.63	1.311	0.16*	1.082	0.63
Group 4:Depressed Non-users	0.926	0.78	0.810	0.33	0.743	0.09
Group 5: Non-depressed Non-users	1	Reference	1	Reference	1	Reference
Age at baseline	1.053	**<.001**	1.065	**<.001**	1.071	**<.001**
Years of education	1.053	**0.04**	1.017	0.38	1.001	0.93
Cerebrovascular disease	1.520	**0.02**	1.443	**0.01**	1.452	**0.004**
Liver disease	1.930	**0.01**	1.451	0.11	1.818	**0.002**
CESD	1.014	0.15	1.016	**0.04**	1.016	**0.01**
SPMSQ	1.450	**<.001**	1.368	**<.001**	1.307	**<.001**

*Covariates not significant in any of the three models were excluded.

†Covariates are adjusted at baseline except for CESD and SPMSQ which were measured at enrollment.

‡Significant difference in hazard ratio when comparing to the depressed non-user group (P<0.05)

Table 3

Cox's PH models for incident dementia comparing antidepressant users to severe depressed non-users.

Parameter*	Model 1 (5-year follow-up)		Model 2 (9-year follow-up)		Model 3 (18 year follow-up)	
	Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value
Group 1:SSRIs	2.214	**0.01**	2.193	**0.003**	2.260	**0.001**
Group 2: Non-SSRIs	1.444	0.18	1.537	0.05	1.616	**0.02**
Group 3: Mixed Group	0.951	0.88	1.193	0.47	1.258	0.27
Group 4: Severely depressed non-users	1	Reference	1	Reference	1	Reference
Group 5:Non-user not depressed	0.679	0.10	0.741	0.12	0.972	0.86
Age at baseline	1.054	**<.001**	1.062	**<.001**	1.066	**<.001**
Years of education	1.058	**0.01**	1.028	0.12	1.010	0.50
Cerebrovascular disease	1.350	0.07	1.286	0.07	1.304	**0.03**
Liver Disease	1.755	**0.02**	1.432	0.10	1.804	**0.001**
SPMSQ	1.472	**<.001**	1.388	**<.001**	1.321	**<.001**

*Variables that were not significant in any of the three models were excluded.

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