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Association between first-line antidepressant use and risk of dementia in older adults: a retrospective cohort study

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Abstract

Background Prior studies suggested that antidepressant use is associated with an increased risk of dementia compared to no use, which is subject to confounding by indication. We aimed to compare the dementia risk among older adults with depression receiving first-line antidepressants (i.e., SSRI/SNRI) versus psychotherapy, which is also considered the first-line therapy for depression.

Methods This retrospective cohort study was conducted using the US Medical Expenditure Panel Survey from 2010 to 2019. We included adults aged ≥ 50 years diagnosed with depression who initiated SSRI/SNRI or psychotherapy. We excluded patients with a dementia diagnosis before the first record of SSRI/SNRI use or psychotherapy. The exposure was the patient's receipt of SSRI/SNRI (identified from self-report questionnaires) or psychotherapy (identified from the Outpatient Visits or Office-Based Medical Provider Visits files). The outcome was a new diagnosis of dementia within 2 years (i.e., survey panel period) identified using ICD-9/ICD-10 codes from the Medical Conditions file. Using a multivariable logistic regression model, we reported adjusted odds ratios (aORs) with 95% confidence intervals (CIs). We also conducted subgroup analyses by patient sex, age group, race/ethnicity, severity of depression, combined use of other non-SSRI/SNRI antidepressants, and presence of underlying cognitive impairment.

Results Among 2,710 eligible patients (mean age = 61 ± 8 , female = 69%, White = 84%), 89% used SSRIs/SNRIs, and 11% received psychotherapy. The SSRI/SNRI users had a higher crude incidence of dementia than the psychotherapy group (16.4% vs. 11.8%), with an aOR of 1.36 (95% CI = 1.06–1.74). Subgroup analyses yielded similar findings as the main analyses, except no significant association for patients who were aged < 65 years (1.23, 95% CI = 0.93–1.62), male (1.34, 95% CI = 0.95–1.90), Black (0.76, 95% CI = 0.48–1.19), had a higher PHQ-2 (1.39, 95% CI = 0.90–2.15), and had underlying cognitive impairment (1.06, 95% CI = 0.80–1.42).

Conclusions Our findings suggested that older adults with depression receiving SSRIs/SNRIs were associated with an increased dementia risk compared to those receiving psychotherapy.

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Key points

- Our findings suggested that SSRI/SNRI use was associated with an increased dementia risk compared to psychotherapy among older adults with depression.
- Subgroup analyses yielded similar findings as the main analyses, except no significant association for patients who were aged < 65 years, male, Black, had a higher PHQ-2 score, and had underlying cognitive impairment.

Why does this matter?

Clinicians should be aware of SSRI/SNRI-associated dementia risk when considering the first-line treatment for older adults with depression. Patient characteristics may also play a critical role in such an association.

Keywords Antidepressants, Psychotherapy, Depression, Dementia, Older adults

Impact statement

We certify that this work is novel. This work is the first to compare first-line antidepressants (i.e., SSRI/SNRI) to an active comparator (i.e., psychotherapy) to reduce confounding by indication instead of comparing antidepressant use to no use in prior studies.

Background

One out of ten older adults aged ≥ 65 years suffers from dementia in the United States (US), and the prevalence dramatically increases with age [1]. The economic burden of dementia is estimated to be high, exceeding \$321 billion (not including \$272 billion in unpaid caregiving) [1]. As such, dementia is among the leading contributors to the global disease burden, which accounts for 4.3% of the number of years lost due to ill health, disability, or early death (i.e., disability-adjusted life years). Furthermore, depression affects approximately 8.4% of US adults, [2] especially those aged 15–49 years [3]. Patients with early-life depression (i.e., onset before the age of 60) have a 2- to 3-fold higher risk of developing dementia, [4] probably through cerebrovascular changes, an increase in glucocorticoids and proinflammatory cytokines, and a decrease in nerve growth factors that lead to hippocampal atrophy and cognitive impairment [5, 6].

Psychotherapy and antidepressants are considered the mainstay treatments for depression [7]. Psychotherapy refers to talking with psychologists, psychiatrists, or other providers to relieve mental health issues, and thus is sometimes called “talk therapy” [8]. Antidepressants are drugs targeting certain neurotransmitters to modulate mood and behavior, of which the mechanism of action differs slightly by classes [9]. Among the antidepressant classes, selective serotonin reuptake inhibitors (SSRI, e.g., fluoxetine) and serotonin norepinephrine reuptake inhibitors (SNRI, e.g., venlafaxine) are considered first-line pharmacological pharmacotherapy due to fewer side effects compared to others such as tricyclic antidepressants (TCAs, e.g., amitriptyline) [10].

Although antidepressants are beneficial for managing depressive symptoms, some studies reported the association between antidepressants and risk of dementia. For example, a meta-analysis found an increased long-term risk (follow-up > 1 year) of dementia associated with antidepressant use compared to no use among older adults [11]. Kodesh et al. also suggested that antidepressant use was associated with a more than 3-fold increased risk of dementia compared to nonusers among older adults, probably due to their anticholinergic side effects [12]. However, the findings were inconsistent in other studies. For instance, Eisch et al. suggested that antidepressants may have cognitive benefits owing to their anti-inflammatory and neurogenic properties in addition to reducing depressive symptoms [13]. Jacob et al. also found that the use of antidepressants was associated with a reduced risk of dementia in patients with moderate or severe depression compared to nonusers of antidepressants [14].

Prior studies are limited by only comparing antidepressant exposure with no exposure, which may be subject to confounding by indication and severity [15]. That is, patients taking antidepressants are likely to suffer from more severe depression than nonusers, while depression itself can be a risk factor for dementia, making separating the drug effect from depression severity challenging [15]. In addition, TCAs are currently second-line pharmacotherapy for depression due to their higher anticholinergic burden that may increase multiple side effects (e.g., cognitive decline) [16]. It may not be appropriate to combine all the classes of antidepressants into one group when evaluating the risk of dementia. Therefore, we aimed to compare the risk of dementia among older adults using SSRIs/SNRIs (i.e., first-line pharmacological treatments) versus those on psychotherapy, adjusting for patients' demographics, socioeconomic status, comorbidities, comedications, and most importantly, the severity of depression to minimize confounding by indication.

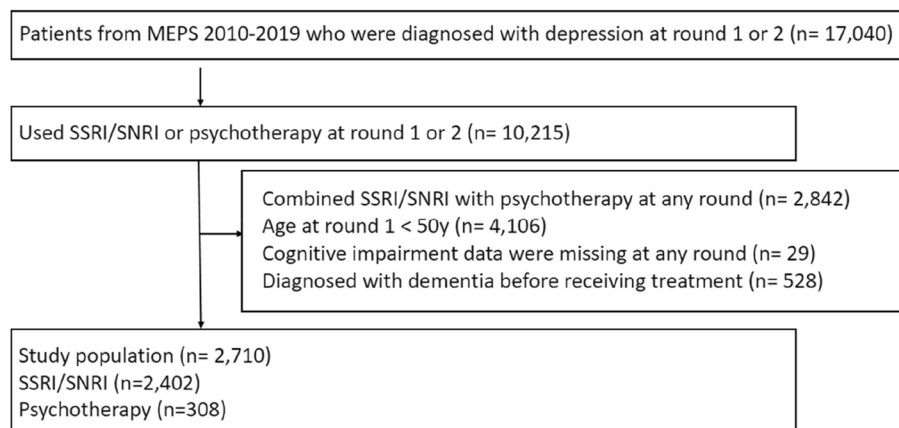


Fig. 1 Study population selection. From the 2010–2019 MEPS data, we identified 17,040 patients diagnosed with depression at round 1 or 2, of which 10,215 patients used SSRI/SNRI at round 1 or 2. Each panel in MEPS data includes 5 rounds within 2 years. The reason for limiting to the first two rounds was to allow at least one year follow-up time for each patient. We excluded patients combining SSRI/SNRI with psychotherapy at any round (n=2,842), aged <50 years at round 1 (n=4,106), missed cognitive impairment data at any round (n=29), and diagnosed with dementia before the index round (n=528). There were 2,710 patients included in our analytical cohort, with 2,402 (89%) using SSRIs/SNRIs and 308 (11%) receiving psychotherapy.

Methods

Data source

This study used the 2010–2019 US Medical Expenditure Panel Survey (MEPS) data, a longitudinal, large-scale survey of noninstitutionalized adults in the US [17]. Each panel covers a two-year period, in which each surveyed household was interviewed five rounds. This survey encompasses information such as individual sociodemographic characteristics, disease diagnoses, comorbidities, and medication use. We selected and merged data from the full-year consolidated file, prescribed medicines file, medical conditions file, and outpatient visits file.

MEPS data is reviewed and approved by the Westat Institutional Review Board (IRB) annually and is established under a multi-project assurance (MPA M-1531) granted by the Office for Protection from Research Risks. After carefully removing individual's identifiable information, an annual series of Public Use Files of de-identified MEPS data are made publicly available to researchers (<https://meps.ahrq.gov/mepsweb/>). Due to the nature of de-identification and public availability of the MEPS data, the University of Florida IRB determined the study exempt and did not require informed consent to participate.

Study design

We conducted a retrospective cohort study restricted to adults aged ≥ 50 years with a depression diagnosis in round 1 or 2 of a two-year panel period to allow at least a 1-year follow-up time. Depression was identified

using International Classification of Disease (ICD) codes (ICD-9: 296.20–296.25, 296.30–296.35, 300.4, 311; positive predictive value [PPV]=92.0%; ICD-10: F32.0–32.9, F33.0–33.3, F33.8, F33.9, F34.1 & F41.2; PPV=91.1%) [18]. We further included those receiving SSRIs/SNRIs or psychotherapy at rounds 1 or 2, with an index round defined as the round when the first SSRI/SNRI or psychotherapy was prescribed. We excluded patients who (1) concomitantly used SSRIs/SNRIs and psychotherapy at any round, (2) had missing cognitive impairment data at all rounds during 2010–2019, and (3) had a dementia diagnosis before the index round. We followed up patients until the dementia outcome occurred or the end of each survey panel period (i.e., two years). Figure 1 depicts the details of the study cohort selection.

Exposure ascertainment

Our exposure of interest was the patient's receipt of SSRIs/SNRIs versus psychotherapy. We identified SSRI/SNRI use from the questionnaires in the prescribed medicines files using therapeutic classification variables from Cerner Multum, Inc. (Appendix Table 1). Psychotherapy used was identified from the Outpatient Visits or Office-Based Medical Provider Visits files.

Outcome ascertainment

We identified the outcome of interest, a new diagnosis of dementia within each two-year survey panel period, using ICD-9 codes (290, 331.0, 331.1, 331.2, 331.82, 331.83, 331.9, 438.0, 780.93) and ICD-10 codes (F00, F01, F03, F04, G30, G31.0, G31.1, G31.8, G31.9, I69.91, R41)

from the Medical Conditions file (Appendix Table 1). The PPV values of using these ICD codes to identify dementia ranged from 73.2 to 93.6% [18].

Confounder ascertainment

We adjusted for confounders associated with both the exposure and the outcome, which were identified based on the literature review and clinical knowledge [19–21]. Using the questionnaires in Full-Year Consolidated files, we measured confounders including age, sex, race/ethnicity, insurance type, marital status, region, poverty, education, Patient Health Questionnaire (PHQ)-2 score, cognitive impairment, smoking, physical activity, and access to healthcare information (i.e., delayed or unable to obtain necessary medical care/prescribed medications). Race/ethnicity was self-reported by study participants. The PHQ-2 score was used to estimate the severity of depression, which assessed the frequency of depressed mood and anhedonia over the past two weeks [22]. We also included comorbidities (cancer, type 2 diabetes, hyperlipidemia, hypertension, ischemic stroke, chronic heart disease, osteoarthritis, Parkinson's disease, anxiety, sleep disorder, schizophrenia, and bipolar disorder) and other medication use (analgesics, benzodiazepines, anxiolytics, sedatives, hypnotics, non-SSRI/SNRI antidepressants, antipsychotics, and antiparkinsonian agents) that were extracted from the medical conditions files and prescribed medicines files, respectively. Operational definitions of the covariates were in Appendix Table 1, and the directed acyclic graph illustrating the relationships among exposure, outcome, and confounders was in Appendix Fig. 1.

Statistical analysis

The statistical analysis for this study comprised the following steps (Appendix Fig. 2). First, we excluded the covariate “type of insurance” since its missingness was too high (90.8%). The proportion of missing information varied from 0.1 to 28.2% across the remaining variables. We then used a multiple imputation approach to address the missingness in the covariates, which imputed multiple sets (i.e., 10) of missing data based on the observed data and pooled the imputed results together in the survey sample [23]. Second, we used multivariable logistic regression (MLR) to estimate the propensity score (PS) of receiving SSRIs/SNRIs vs. psychotherapy (i.e., the conditional probability of receiving SSRIs/SNRIs relative to psychotherapy given a set of covariates including patients' sex, age, race/ethnicity, region, education, poverty, marital status, physical inactivity, smoking, access to healthcare, severity of depression, comorbidities and comedICATIONS mentioned above). Third, we trimmed the

analytical cohort using the 5th percentile in the treated group as the lower limit and the 95th percentile in the untreated group as the upper limit [24]. Fourth, we balanced the characteristics between patients receiving SSRIs/SNRIs and those receiving psychotherapy using the stabilized inverse probability treatment weighting (sIPTW) approach, which preserves the sample size of the original data and avoids underestimating the variance compared to IPTW [25]. We presented the baseline characteristics between the SSRI/SNRI and psychotherapy groups before and after sIPTW using the mean (standard deviation [SD]) for continuous variables and frequency (percentage [%]) for categorical variables. Differences in baseline characteristics between the two groups were compared using the absolute standardized mean difference (ASMD). An $ASMD \leq 0.10$ suggests balance in the given variable between the groups.

Using the sIPTW-adjusted MLR, we were able to estimate the average treatment effect in the treated (ATT) [26]. Given that MEPS uses a complex survey design with clustering, stratification, and weights, the MLR was performed using the SURVEYLOGISTIC procedure in SAS to obtain the population ATT [27]. We multiplied the sIPTW by the survey weight to form a composite weight and applied it to the WEIGHT option of the SURVEYLOGISTIC procedure as done in prior studies [28, 29]. The dependent variable of the MLR was a new diagnosis of dementia (i.e., yes or no). The independent variables of the MLR included not only exposure (i.e., receiving SSRI/SNRI vs. psychotherapy) but the unbalanced covariates ($ASMD > 0.1$) after sIPTW (i.e., doubly robust approach) [30]. We reported the crude odds ratio (OR) and adjusted OR (aOR) with 95% confidence intervals (CI) to assess the association between SSRI/SNRI use and the risk of dementia using psychotherapy as the comparison group. We also reported the marginal effect, defined as the change in the probability of dementia when using SSRIs/SNRIs compared to psychotherapy after holding all other covariates constant. Similarly, we used the SURVEYLOGISTIC procedure when estimating the marginal effect in order to show the population average treatment effect (ATE) [31]. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Subgroup and sensitivity analyses

To evaluate the heterogeneity in the drug effect among different patient subgroups, we grouped patients by sex (i.e., male and female), age group (i.e., < 65 y and ≥ 65 y), race/ethnicity (i.e., White and Black), severity of depression (i.e., PHQ-2 score 0–2 and 3–6), concomitant use of non-SSRI/SNRI antidepressants (i.e., yes and no), and underlying cognitive impairment (i.e., yes and no). Then,

we repeated all the steps in the main analysis in each subgroup.

To test the robustness of our findings, we performed two sensitivity analyses. First, we used a 1:1 greedy nearest neighbor PS matching approach to match patients using SSRI/SNRI to those receiving psychotherapy. Similar to the main analysis, PS matching with the PROC SURVEYLOGISTIC procedure allows us to estimate the population ATT. Second, we used a subset of covariates (excluding comedications as this information may be susceptible to recall bias) to estimate the PS and repeated the sIPTW approach.

Results

Baseline characteristics

As shown in Fig. 1, a total of 2,710 patients were eligible for the analysis, with 89% receiving SSRIs/SNRIs and 11% receiving psychotherapy. The PSs of the SSRI/SNRI and psychotherapy groups highly overlapped with each other after trimming (Fig. 2), and most covariates were balanced between the SSRI/SNRI users and psychotherapy users (Table 1). The mean age was 60.5 ± 7.8 years for patients using SSRIs/SNRIs and 60.8 ± 8.4 years for patients using psychotherapy. The majority of the individuals were White in the SSRIs/SNRIs group (84.9%) and the psychotherapy group (82.3%). The median PHQ-2 score was 1.4 for both groups. The proportions of patients with underlying cognitive impairment were 20.4% and 21.5% in the SSRI/SNRI and psychotherapy groups, respectively.

Association between antidepressant use and the risk of dementia, main analysis

In Table 2, the crude incidence of dementia within two years was 16.4% in SSRI/SNRI users and 11.8% in the psychotherapy group. After adjusting for patients' baseline characteristics, the aOR was 1.36 (95% CI = 1.06–1.74), and the marginal effect suggested that receipt of SSRIs/SNRIs was associated with a 31.0% (95% CI = 6.6–55.3%) increased risk of dementia within two years compared to those receiving psychotherapy among older adults with depression after adjusting for the confounders (i.e., age, sex, race/ethnicity, insurance type, marital status, region, poverty, education, PHQ-2 score, cognitive impairment, smoking, physical activity, access to healthcare information, comorbidities, and comedications).

Association between antidepressant use and the risk of dementia, subgroup and sensitivity analyses

Most subgroup analyses reported consistent results with the main analysis, except for patients who were aged < 65

years, male, Black, had a PHQ-2 score of 3–6, and had underlying cognitive impairment, for whom the adjusted ORs (95% CI) were 1.23 (0.93–1.62), 1.34 (0.95–1.90), 0.76 (0.48–1.19), 1.39 (0.90–2.15), and 1.06 (0.80–1.42), respectively. The sensitivity analyses yielded similar findings as the main analysis. The adjusted ORs (95% CI) were 1.27 (1.18–1.37) using the 1:1 PS matching and 1.12 (1.05–1.20) when removing comedications from the PS calculation.

Discussion

In this retrospective cohort study using nationally representative survey data in the US, we found that older adults with depression receiving SSRIs/SNRIs were associated with a 31% increased risk of dementia within two years compared to those receiving psychotherapy after adjusting for patient characteristics such as age, sex, race/ethnicity, depression severity, underlying cognitive impairment, comorbidities, and concomitant drugs. Most subgroup analyses yielded similar results, except for patients who were aged < 65 years, male, Black, had a PHQ-2 score of 3–6, and had underlying cognitive impairment, which did not show significant differences in the risk of dementia between SSRI/SNRI use and psychotherapy.

Unlike previous studies largely comparing antidepressant users with nonusers, our study adopted the active comparison group approach to reduce confounding by indication and severity in older adults with depression. Our findings were consistent with some of the prior studies. For example, a meta-analysis including observational studies with at least a 1-year follow-up period showed that SSRI use was associated with an increased risk of dementia compared to no SSRI use, with a pooled risk ratio (RR) of 1.75 (95% CI: 1.03–2.96). However, the heterogeneity in the meta-analysis was extremely high, and one out of five included studies suggested that SSRI use was associated with a lower risk of dementia (RR: 0.58, 95% CI: 0.50–0.68) [11]. Another study by Lee et al., restricted to older adults with depression, found that SSRI use was associated with an increased risk of incident dementia, with an adjusted OR of 2.48 (95% CI: 2.27–2.71) [32]. Nonetheless, Peakman et al., 2020 [33] and Goveas et al., 2012 [34] pointed out that even though antidepressant use was found to be associated with the risk of dementia (adjusted hazard ratio [HR]: 1.32 [95% CI: 1.01–1.74] and 1.69 [95% CI: 1.21–2.35], respectively), an association was not found for SSRIs (adjusted HR: 1.07 [95% CI: 0.91–1.25] and 1.50 [95% CI: 0.89–2.53], respectively). Instead, this association may be attributed to TCAs, which were found to be associated with incident dementia (adjusted HR: 1.75 [95% CI: 1.05–2.91]

Table 1 Baseline characteristics of the study population: 2010–2019 Medical Expenditure Panel Survey Data

	Unweighted sample ^a (n=2,710)			Weighted sample using sIPTW ^b (n=1,858)		
	SSRIs/SNRIs (n=2,402)	Psychotherapy (n=308)	ASMD	SSRIs/SNRIs (n=1,652)	Psychotherapy (n=206)	ASMD
Age, mean (SD)	63 (9.2)	59.2 (8.0)	0.43*	60.5 (7.8)	60.8 (8.4)	-0.03
PHQ-2, median (IQR)	1.4 (1.7)	1.8 (1.9)	0.21*	1.4 (1.8)	1.4 (1.8)	0.04
Cognitive impairment, n (%)	451 (18.8)	90 (29.2)	0.25*	337 (20.4)	44 (21.5)	-0.03
Female, n (%)	1688 (70.3)	187 (60.7)	0.20*	1133 (68.6)	143 (69.3)	-0.02
Race, n (%)						
White	1783 (87.0)	211 (78.7)	0.22*	1404 (84.9)	170 (82.3)	0.07
Black	161 (7.9)	42 (15.7)	0.24*	153 (9.3)	26 (12.7)	-0.11*
Others	106 (5.2)	15 (5.6)	0.02	96 (5.8)	10 (5.1)	0.03
Hispanic, n (%)	271 (11.3)	34 (11.0)	0.01	196 (11.9)	24 (11.8)	0
Region, n (%)						
Northeast	356 (14.8)	85 (27.6)	0.32*	286 (17.3)	33 (16.2)	0.03
Midwest	593 (24.7)	79 (25.6)	0.02	446 (27)	55 (26.5)	0.01
South	922 (38.4)	74 (24.0)	0.31*	512 (31)	71 (34.5)	-0.07
West	531 (22.1)	70 (22.7)	0.01	409 (24.7)	47 (22.8)	0.05
Education, n (%)						
No degree	284 (15.4)	29 (11.9)	0.10	223 (13.5)	32 (15.5)	-0.06
General education development	87 (4.7)	11 (4.5)	0.01	77 (4.7)	11 (5.4)	-0.03
High school	832 (45.0)	82 (33.6)	0.24*	657 (39.7)	74 (36.1)	0.08
Higher education	473 (25.6)	83 (34.0)	0.18*	509 (30.8)	67 (32.5)	-0.04
Others	171 (9.3)	39 (16.0)	0.20*	186 (11.3)	22 (10.6)	0.02
Poverty, n (%)						
Poor/negative	335 (13.9)	67 (21.8)	0.20*	252 (15.2)	33 (16.2)	-0.03
Near poor	133 (5.5)	17 (5.5)	0.00	83 (5)	12 (6)	-0.04
Low income	358 (14.9)	47 (15.3)	0.01	247 (15)	34 (16.6)	-0.05
Middle income	716 (29.8)	65 (21.1)	0.20*	421 (25.5)	54 (26.1)	-0.01
High income	860 (35.8)	112 (36.4)	0.01	650 (39.3)	72 (35.1)	0.09
Marital status, n (%)						
Married	1323 (55.1)	131 (42.5)	0.25*	882 (53.4)	107 (51.7)	0.03
Separated, Widowed or Divorced	175 (7.3)	48 (15.6)	0.26*	131 (7.9)	17 (8.1)	-0.01
Never married	904 (37.6)	129 (41.9)	0.09	639 (38.7)	83 (40.2)	-0.03
Physical inactivity, n (%)	891 (37.1)	119 (38.6)	0.03	600 (36.3)	81 (39.4)	-0.06
Smoking, n (%)	356 (18.5)	52 (21.9)	0.09	325 (19.7)	30 (14.8)	0.13*
Limited access to health care, n (%)	224 (12.9)	36 (16.9)	0.11*	242 (14.6)	26 (12.4)	0.06
Comorbidities, n (%)						
Cancer	14 (0.6)	2 (0.6)	0.01	9 (0.5)	2 (0.9)	-0.04
Type 2 diabetes	41 (1.7)	5 (1.6)	0.01	30 (1.8)	5 (2.4)	-0.04
Hyperlipidemia	67 (2.8)	13 (4.2)	0.08	57 (3.5)	12 (5.9)	-0.11*
Hypertension	61 (2.5)	7 (2.3)	0.02	42 (2.6)	7 (3.5)	-0.05
Ischemic stroke	1 (0)	0 (0)	0.03	0 (0)	0 (0)	0
Chronic heart disease	18 (0.7)	1 (0.3)	0.06	9 (0.5)	1 (0.7)	-0.02
Osteoarthritis	29 (1.2)	3 (1)	0.02	19 (1.2)	1 (0.6)	0.07
Parkinson's disease	1 (0)	0 (0)	0.03	0 (0)	0 (0)	0
Anxiety	373 (15.5)	27 (8.8)	0.21*	177 (10.7)	15 (7.3)	0.12*
Sleep disorder	23 (1.0)	6 (1.9)	0.08	19 (1.1)	2 (0.8)	0.03
Schizophrenia	0 (0)	3 (1.0)	0.14*	0 (0)	0 (0)	0
Bipolar disorder	14 (0.6)	14 (4.5)	0.25*	6 (0.3)	0 (0.1)	0.06

Table 1 (continued)

	Unweighted sample ^a (n=2,710)			Weighted sample using sIPTW ^a (n=1,858)		
	SSRIs/SNRIs (n=2,402)	Psychotherapy (n=308)	ASMD	SSRIs/SNRIs (n=1,652)	Psychotherapy (n=206)	ASMD
Comedications, n (%)						
Analgesics	201 (8.4)	27 (8.8)	0.01	146 (8.9)	20 (9.5)	-0.02
Benzodiazepines	56 (2.3)	14 (4.5)	0.12*	43 (2.6)	6 (3)	-0.02
Anxiolytics, sedatives, and hypnotics	62 (2.6)	6 (1.9)	0.04	40 (2.4)	7 (3.3)	-0.05
Antidepressants other than SSRI/SNRI	46 (1.9)	12 (3.9)	0.12*	33 (2)	3 (1.4)	0.04
Antipsychotics	13 (0.5)	17 (5.5)	0.29*	2 (0.1)	1 (0.4)	-0.06
Antiparkinsonian agents	15 (0.6)	4 (1.3)	0.07	13 (0.8)	0 (0)	0.13*

Abbreviation: *sIPTW* Stabilized inverse probability treatment weighting, *SSRI* Selective serotonin reuptake inhibitors, *SNRI* Serotonin and norepinephrine reuptake inhibitors, *SD* Standard deviation, *ASMD* Absolute standardized mean difference

* An ASMD ≤ 0.10 suggests balance in the given variable between the groups.

^a Results shown in Table 1 were calculated within the survey sample.

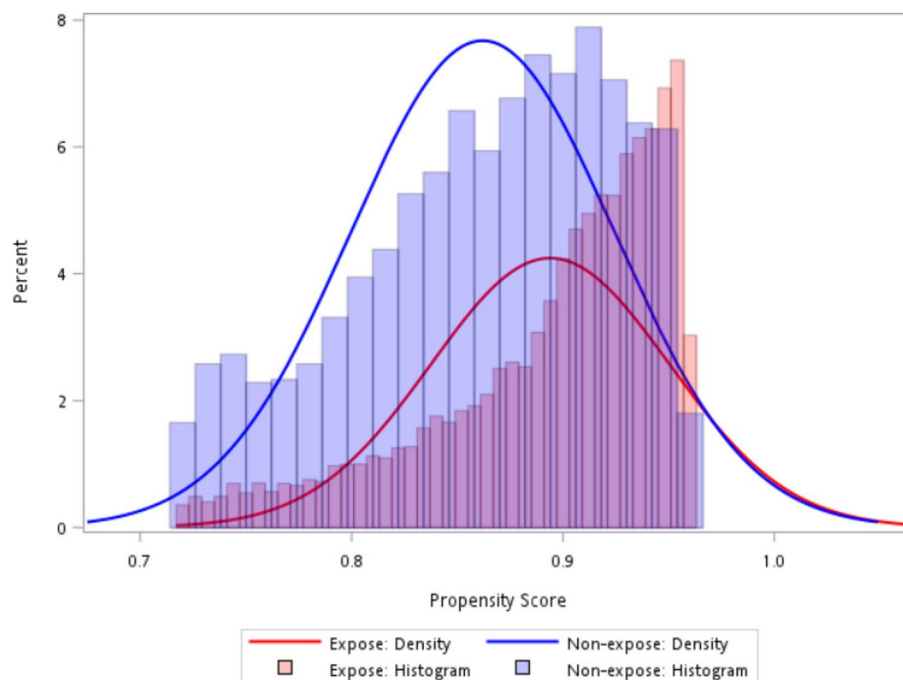


Fig. 2 Distribution of propensity scores in the exposed (i.e., SSRI/SNRI) and unexposed (i.e., psychotherapy) groups. This figure shows that the propensity scores of the SSRI/SNRI and psychotherapy groups highly overlapped with each other after trimming

reported by Goveas et al., 2012). Other reasons contributing to the conflicting findings from the existing studies include prior claim-based studies unable to include the severity of depression and cognitive impairment status in the analysis. Our survey data analysis addressed these issues by including patients’ PHQ-2 score, co-use of other antidepressants, and underlying cognitive impairment.

In the subgroup analyses, we found that the association between SSRI/SNRI use and dementia risk did not exist in patients with a higher PHQ-2 score. Patients

with a higher PHQ-2 score might reflect those with more severe depression or uncontrolled depression, which may confound the drug effect [35]. That is, the progression of depression [36] may play a critical role in the risk of dementia, and thus masking the effect of SSRIs/SNRIs. The association also did not exist in patients with underlying cognitive impairment, which is probably because clinicians are more concerned about the risk of dementia if patients have prior cognitive impairment, and thus psychotherapy is preferred to SSRI/SNRI use [11]. However,

Table 2 Odds ratios of dementia among older adults with depression using selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs) compared to those receiving psychotherapy

	Crude incidence (%) ^b		OR (95% CI) ^c		Marginal effect (%) ^b
	SSRI/SNRI	Psychotherapy	Crude	Adjusted	
Main analysis: SSRI/SNRI vs. psychotherapy	16.4	11.8	1.46 (0.97, 2.20)	1.36 (1.06, 1.74) ^a	31.0 (6.6, 55.3) ^a
Subgroup analysis stratified by					
Age					
< 65 years	14.5	12.6	1.18 (0.75, 1.87)	1.23 (0.93, 1.62)	20.6 (-6.6, 47.7)
≥ 65 years	19.3	9.1	2.38 (1.05, 5.41) ^a	1.73 (1.09, 2.75) ^a	54.6 (10.2, 98.9) ^a
Sex					
Male	17.5	13.0	1.42 (0.81, 2.50)	1.34 (0.95, 1.90)	29.5 (-3.5, 62.4)
Female	15.9	11.1	1.52 (0.91, 2.54)	1.38 (1.02, 1.86) ^a	32.3 (3.2, 61.5) ^a
Race					
White	15.0	8.9	1.81 (1.00, 3.27)	1.48 (1.10, 1.98) ^a	38.7 (12.1, 65.4) ^a
Black	18.1	17.6	1.04 (0.62, 1.74)	0.76 (0.48, 1.19)	-25.5 (-54.1, 3.1)
PHQ-2 score					
0-2	15.6	11.7	1.39 (0.83, 2.33)	1.35 (1.00, 1.81) ^a	29.8 (1.2, 58.3) ^a
3-6	23.4	14.9	1.75 (0.96, 3.20)	1.39 (0.90, 2.15)	33.9 (-0.8, 68.6)
Concomitant antidepressants other than SSRI/SNRI					
Yes	31.3	5.6	7.67 (6.93, 8.49) ^a	3.74 (1.55, 9.07) ^a	155.3 (153.3, 157.3) ^a
No	16.1	12.0	1.41 (0.94, 2.13)	1.34 (1.04, 1.73) ^a	29.5 (5.1, 53.8) ^a
Underlying cognitive impairment					
Yes	21.4	15.5	1.49 (0.99, 2.24)	1.06 (0.80, 1.42)	6.3 (-18.1, 30.7)
No	15.4	10.7	1.51 (0.89, 2.57)	1.49 (1.10, 2.03) ^a	39.9 (9.9, 69.9) ^a
Sensitivity analyses					
1:1 nearest neighbor PS matching	16.4	11.8	1.46 (0.97, 2.20)	1.27 (1.18, 1.37) ^a	28.0 (5.1, 50.9) ^a
Removing comedications from PS estimation	16.4	11.8	1.46 (0.97, 2.20)	1.12 (1.05, 1.20) ^a	22.0 (9.1, 34.8) ^a

Abbreviations: CI Confidence interval, OR odds ratio, PS Propensity score, RRD Relative risk difference, SNRI Serotonin and norepinephrine reuptake inhibitors, SSRI Selective serotonin reuptake inhibitors

^a Statistically significant

^b The crude incidence represents the incidence of dementia in the overall population (accounted for the survey design)

^c The odds ratio represents the population average treatment effect in the treated (accounted for the survey design)

^b The marginal effect represents the population average treatment effect (accounted for the survey design)

this group of patients is at high risk of dementia, which may lead to mitigation of the risk in the SSRI/SNRI group. The association also did not exist in Black adults, probably because Black adults are less likely to receive SSRI/SNRI than White adults even though they have similar severity of depression, [37] which may dilute the drug effect as well. Finally, the reason for no association among these subgroups could also be due to the small sample sizes after stratification.

There are some limitations in our study. First, we used MEPS data, which only follow a patient for at most 2 years, which may not be long enough for dementia to occur and underestimate the risk of dementia [38]. However, in a population-based study with a mean follow-up of 8 years, the incidence of dementia was 13% among older adults with depression, [39] similar to our findings. Second, we were

unable to identify incident new users of SSRIs/SNRIs and psychotherapy due to the lack of a washout period. Therefore, we could not address the depletion of susceptibles, [40] meaning that patients who were using SSRI/SNRI may be the ones who were less likely to incur dementia. Third, although we conducted several subgroup analyses to address potential heterogeneity in the drug effect across patient subgroups, we were unable to include potential confounders such as duration of depression [37]. Fourth, death was a competing risk in our study (i.e., if patients died, then they would not experience dementia afterwards), yet we were unable to measure this using MEPS data. Fifth, dose and duration of SSRI/SNRI use may be associated with dementia risk, yet MEPS data does not provide such information.

Conclusion

Our findings provide valuable insight into the complex association among depression, antidepressants, and risk of dementia, providing additional evidence for clinicians while prescribing antidepressants for patients with depression. Future longitudinal studies are warranted to allow the identification of new users of antidepressants and the evaluation of long-term dementia risk.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-023-04475-z>.

Additional file 1: Appendix Figure 1. Directed acyclic graph illustrating the relationships among exposure, outcome, and confounders. **Appendix Figure 2.** Detailed steps of the statistical analysis. **Appendix Table 1.** Variables included in our study.

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None.

Authors' contributions

GHMW developed the research question. GHMW, WHC, TZ, and SHC performed the data analysis. GHMW drafted the manuscript, and WHC, TZ, SHC, HS, JG, and WHL revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials

All data analyzed in this article are publicly available at https://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files.jsp.

Declarations

Ethics approval and consent to participate

The study used Medical Expenditure Panel Survey (MEPS) data, which is reviewed and approved by the Westat Institutional Review Board (IRB) annually and is established under a multi-project assurance (MPA M-1531) granted by the Office for Protection from Research Risks. After carefully removing individual's identifiable information, an annual series of Public Use Files of de-identified MEPS data are made publicly available to researchers (<https://meps.ahrq.gov/mepsweb/>). Due to the nature of de-identification and public availability of the MEPS data, the University of Florida IRB determined the study exempt and did not require informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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