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Antidepressant Use and Cognitive Deficits in Older Men: Addressing Confounding by Indications Using Different Methods

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Abstract

Purpose—Antidepressant use has been associated with cognitive impairment in older persons. This study sought to examine whether this association might reflect an indication bias.

Methods—544 community-dwelling hypertensive men aged ≥ 65 years completed the Hopkins Verbal Learning Test (HVLT) at baseline and one year. Antidepressant medications were ascertained using medical records. Potential confounding by indications was examined by adjusting for depression-related diagnoses and severity of depression symptoms using multiple linear regression (MLR), a propensity-score (PS) and a structural equation model (SEM).

Results—Before adjusting for the indications, a one unit cumulative exposure to antidepressants was associated with −1.00 (95% Confidence Interval (CI): −1.94, −0.06) point lower HVLT score. After adjusting for the indications using MLR or a PS, the association diminished to −0.48 (95% CI: −0.62, 1.58) and −0.58 (95% CI: −0.60, 1.58), respectively. The most clinically interpretable empirical SEM with adequate fit involves both direct and indirect paths of the two indications. Depression-related diagnoses and depression symptoms significantly predict antidepressant use ($P < 0.05$). Their total standardized path coefficients on HVLT score were twice (0.073) or as large (0.034) as the antidepressant use (0.035).

Conclusion—The apparent association between antidepressant use and memory deficit in older persons may be confounded by indications. SEM offers a heuristic empirical method for examining confounding by indications, but not quantitatively superior bias reduction compared to conventional methods.

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Keywords

Antidepressant use; confounding by indication; structural equation modeling; elderly; cognitive deficit; multiple linear regression

INTRODUCTION

Observational studies of adverse drug effects face a challenge in ascertaining the causation of an observed association – confounding by indications or reasons for prescribing. When an adverse health outcome is observed, the drugs prescribed to treat a disease may be claimed as the cause, while in fact the underlying disease that triggered the drug treatment is responsible (1–3). The source of this bias can be traced to a study design defect, lack of randomization in treatment assignment. As a result, an observed “treatment effect” may reflect the differences in key population characteristics that affect both the probability of receiving the treatment and risk of the outcome, rather than the treatment under study. Due to the inability to pre-balance these characteristics at the design stage, observational studies must address such a potential bias analytically (1, 2).

The most common analytical method to control confounding by indications is to employ a multivariable method, such as multiple linear regression (MLR), in which the identified “indications” or their surrogates are included as covariates. The adjusted effect estimate for drug use is then conditional on the observed values of these covariates or as a weighted average of them (1, 2) and hence, free of indication bias. While such a direct modeling adjustment is simple and intuitive, treating the indication as regular confounders has several limitations. First and foremost, the temporal precedence of the indications to the drug use can not be realized in a conventional regression context, where both are treated as equally important independent variables. In addition, due to lack of specific clinical assessments, observational studies often have to rely on multiple non-specific measures as surrogates for indications for drug prescribing, which makes regression adjustment scientifically dubious and statistically inefficient (2–4).

To move towards causality, a two-step propensity score (PS) method was developed (2, 4, 5). First, a PS, or conditional probability, of receiving a specific drug given a set of predictors is estimated. Then in the hypothesis testing stage, the estimated PS is used as a covariate, or a stratification or matching variable, to control for confounding in the multivariable model of the relationship between drug exposure and study outcome. Conceptually the PS is expected to increase the validity (by pre-balancing observed confounders between exposure groups) and efficiency (by reducing number of parameters) of regression models. However, studies have not always found it superior to traditional multivariable adjustments (5).

Path analysis is a type of structural equation modeling (SEM) that tests statistical models among observed variables using covariance structures. Although sharing many properties with traditional MLR, path analysis has several unique features. First, it allows for explicit specification of the directionality and hierarchy of several hypothesized “causal” relationships (6–8). Second, it recognizes the imperfect nature of measurements by directly

modeling, rather than ignoring, measurement errors, and by providing multiple model fit statistics, including model chi-square, Root Mean Squared Error of Approximation (RMSEA) and Comparative Fit Index (CFI). Finally, it typically employs a graphical path diagram as a starting point to delineate theoretically complex (causal or non-causal) relationships. Estimates for the specified relationships and model fit are then derived by solving a set of simultaneous equations. Unlike the MLR and PS modeling, the use of SEM in the medical field is relatively limited (7, 9).

In this study, we illustrate how conventional MLR, PS and SEM can be used to address potential confounding by indication surrounding the relationship between antidepressant use and cognitive impairment using data from a cohort of community-dwelling older persons. Antidepressant medications, especially the tricyclic agents, have been associated with cognitive impairment in the elderly (10, 11). Although recent randomized trials demonstrated potential cognitive benefits of antidepressant medications in treating major depressive disorders (12, 13), little is known about their long-term cognitive outcome in older persons living in the community, who often suffer from mild to moderate depressive symptoms, but multiple other chronic conditions (14, 15). Our hypothesis was that the apparent relationship between antidepressant use and cognitive impairment observed in the elderly may reflect potential confounding by underlying depression or the severity of depressive symptoms and would therefore diminish after appropriate adjustment for such covariates.

METHODS

Participants

The Connecticut Veterans Longitudinal Cohort consisted of 767 community-dwelling older persons aged ≥ 65 years. The cohort was originally assembled at a Veterans Administration (VA) primary care clinic between July 2000 and August 2001. Data on demographic profiles, health-behaviors, comorbidities, blood pressure readings, cognitive and physical functioning were collected at baseline and at one year follow-up. The study protocol was approved by the Yale University School of Medicine institutional review board and the VA Connecticut Healthcare System Human Subjects Subcommittee and has been described previously (17, 18). In 2005, additional data were collected on medications from a subset of 544 male cohort members with diagnosed hypertension. Prescription and over-the-counter medications were abstracted from medical records by a research assistant every three months. We selected this subcohort as study sample to take advantage of its augmented medication data. In addition, hypertension is not only highly prevalent in older adults but also typical of complex comorbidity profile (including non-major depression) and medication regimens (14, 15). Hence, it is well suited for addressing confounding by indication in real-world primary care settings.

Outcome measures

The study outcome, cognitive function, was measured using a subscale of the Hopkins Verbal Learning Test (HVLT) (19, 20), which assesses short-term memory using three trials of immediate free recall of 12 words, with scores ranging from 0 (worst) to 36 (best). The

test was administered by trained research personnel following a standardized protocol, first at baseline and then at one year follow-up. We focused on short-term memory as the outcome because it represents a core area of higher brain function that is affected in Alzheimer's dementia (21) and is sensitive to drugs that act specifically on the underlying neurotransmitting mechanism of the disease—the central acetylcholinergic system (18, 20–22).

Antidepressant and other medication use

Antidepressant medications included tricyclics (amitriptyline, doxepine, imipramine, nortriptyline and desipramine), selective serotonin reuptake inhibitors (SSRIs, including citalopram, fluoxetine, paroxetine and sertraline) and atypical agents (bupropion, mirtazapine, nefazodone, trazodone and venlafaxine). Due to the lack of data on dose and duration of medication use, we counted the total numbers of antidepressant drugs across the four quarters and then divided the sum by four to represent approximate 3-month cumulative exposure. For example, use of one antidepressant agent in four quarters or four different agents in a single quarter would give the same quantity of cumulative exposure. We also defined a binary indicator for sensitivity analyses, *ever versus never* use of antidepressants during the one-year period, regardless of the numbers or frequencies of these prescriptions.

Using the same approach, we defined other drug uses for sensitivity analyses. A sedative group encompassed benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, temazepam and triazolam), barbiturates and buspirone; whereas an antipsychotic group included chlorpromazine, olanzapine, perphenazine, prochlorperazine, quetiapine, risperidone and thioridazine. These medications are frequently prescribed to depressed patients for co-existing anxiety, insomnia or behavioral problems (10, 14, 22–24). Therefore, their relationships with cognitive impairment are expected to diminish after adjusting for the indications for antidepressant prescribing as well. On the contrary, antihypertensives (including angiotensin converting enzyme inhibitors and angiotensin receptor blockers, beta-blockers, calcium-channel blockers, diuretics and centrally-acting agents) (16, 18, 25) and anticholinergics (defined using a clinician-rated anticholinergic score ≥ 1) (22) are therapeutically disparate classes not intended to treat depression. Accordingly, their association with cognitive impairment should not be affected by adjusting for depression. This may be especially true for anticholinergics, which have been consistently linked to adverse cognitive effects in both human and animal studies (18, 21, 22).

Indications for antidepressant prescribing

We used two depression-specific measures to represent potential indications for antidepressant prescribing based on clinical knowledge. A diagnosis of depression or related psychiatric conditions (abbreviated hereafter as depression-related diagnosis), including post-traumatic stress disorders, anxiety or alcohol abuse or dependence, were abstracted from medical records and used to define the primary indication. Inclusion of related psychiatric conditions that often co-exist with depression may increase the tolerance of the primary indication against potential misdiagnoses or coding error (14, 26). The secondary indication is severity of depressive symptoms, measured with the 11-item, self-reported

Center for Epidemiologic Studies-Depression scale (CES-D) (27). Adjusting for both depression-related diagnoses and symptom severity enhances the ability of observational studies to control indication bias (3).

Potential confounders

We collected data on potential confounders through interviews with patients and a review of their medical records. Demographic factors included age, education, race and living arrangement. Health-behaviors included alcohol use and smoking. Activities of daily living were assessed on the seven basic items from Older Americans Resources and Services (28). Comorbid medical conditions were measured using the Charlson Comorbidity Index (CCI) (29). Sitting systolic and diastolic blood pressures were taken at baseline and used to define a 4-level severity score compatible to the staging classification proposed by national guidelines (16), with 1 indicating normal blood pressure and 4 indicating severe hypertension. Adjustment for global comorbidity measures has shown to help eliminate indication bias of an observed association between antidepressant use and pneumonia (30).

Statistical analyses

Three different multivariable methods were used to examine the relationship between antidepressant use and the HVLIT score: conventional MLR, PS and SEM. First, to establish a common baseline for comparing methods, a bivariate MLR model including only the cumulative antidepressant exposure as a sole predictor was fit. Then, covariates were introduced into the model hierarchically, first including only the demographic and behavioral factors, and then adding the two comorbidity measures. The model including all the above-mentioned covariates was used as the “Reference” model, against which different adjustment strategies were evaluated.

Next, two alternative strategies were adopted to address potential confounding by indications. The conventional MLR strategy simply added the depression-related diagnoses, and then both the depression-related diagnoses and CES-D score (referred hereafter as Index MLR) to the reference model; whereas the PS strategy involved two steps. In the first step, a PS for initial antidepressant prescribing was estimated for each participant using a logistic regression model, in which antidepressant use at baseline (yes versus no) was regressed on a set of potential predictors, including depression-related diagnoses, CES-D score, systolic and diastolic blood pressure and indicators for eight individual comorbidities. Then the estimated PS was added to the reference model as an ordinal covariate (4, 5), with and without including the two depression-specific indications.

In the SEM context, we first specified a baseline model by allowing both direct and indirect (via mediation of antidepressant exposure) paths from the two indications (exogenous variables), i.e., depression related diagnoses and CES-D score, to the HVLIT score (endogenous variable). This model represents our *a priori* hypothesis that at least part of the observed antidepressant “effect” was attributable to its indications or underlying “causes”, depression (6, 7).

Next, we evaluated alternative models by expanding or trimming the baseline model (6–8). Under the no indication bias assumption, we omitted the mediation paths from the two indications to the antidepressant exposure and kept only their direct paths to the HVLTL score (equivalent to the index MLR). Under the maximum indication bias assumption, we removed the direct paths from the two indications to the HVLTL score while keeping their mediation paths via antidepressant exposure. Between these two boundary scenarios, we explored alternative mediation loops by removing the path from the secondary indication, CES-D score, to antidepressant exposure, and by adding the two global comorbidity measures as extra exogenous variables.

We performed sensitivity analyses to assess the robustness of the primary models. First, we refit the reference and index MLR models by substituting the other drug groups and the binary (*ever versus never*) antidepressant use, respectively, for the cumulative antidepressant exposure as a predictor. Second, we refit the PS-adjusted model using a new PS estimated with additional demographic (age and living condition) and health-behavior (alcohol and tobacco use) covariates. Finally, we fitted a “reverse causality” model by specifying the antidepressant exposure as a “cause” (i.e., exogenous variable) and each indication as a mediator (6–8, 33), and a “counterfactual” indication model by substituting the two global comorbidity measures for depression-related diagnoses and the CES-D score as mediators.

Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC). All the models were estimated using maximum likelihood-based procedures, including PROC GENMOD with identity link and normal error distribution for MLR and PS models, and PROC CALIS for SEM (31, 32). The (unstandardized) effect estimates and 95% confidence intervals (CI) for antidepressant exposure, depression-related diagnoses and the CES-D score, and their *percent changes* between comparison models were used to quantify indication bias (4, 6, 31, 32). Improvement in model fit between nested models was assessed using likelihood ratio (LR) chi-square test (χ^2), with degree of freedom (df) equaling the number of added (or dropped) parameters. For SEM, the total standardized path coefficients (of direct and indirect paths) were also calculated (6–8, 32), and the overall model chi-square (χ^2_M , with df_M equaling number of free parameters), RMSEA and CFI were checked to identify globally χ^2_M unfit (e.g., $\chi^2_M < 0.05$ or RMSEA > 0.10) or scientifically nuisance (e.g., $df_M = 0$) models (6–8, 32). The hypotheses were tested at a two-sided significance level of $\alpha = 0.05$.

RESULTS

Baseline characteristics and antidepressant use during follow-up

At baseline, the study cohort had mild to moderate hypertension severity, a high level of functional autonomy and a lower level of depressive symptoms (Table 1). One hundred and twenty (22.1%) participants had a depression-related diagnosis and 85 (15.6%) were prescribed antidepressants. The most frequent antidepressants are sertraline (5.2%), amitriptyline (2.8%), nortriptyline (1.8%), trazodone (1.5%) and fluoxetine (1.3%). During the one-year follow-up period, 107 (19.7%) participants were prescribed at least one antidepressant, ranging from 10.1% to 18.8% across 4 quarterly intervals. The majority

(n=58, 54.2%) used antidepressants in three or four quarters while 23.4% (n=25) in two and 22.4% (n=24) in a single quarter.

Relationship between antidepressant use and the HVLTL based on MLR and PS adjustment

Table 2 summarizes a serial MLR models of the HVLTL adjusted for potential risk factors, except the two depression-specific indications. After fully accounting for these covariates (model 3, the reference model), cumulative antidepressant exposure remained independently associated with a lower HVLTL score (-1.0 ; 95% CI: $-1.9 - -0.06$; $P<0.05$).

Table 3 extends the reference model in two ways. The association diminished by 44% (model 4.1) and 52% (model 4.2) after direct adjustment for the two indications, and by 42% (model 5.1) and 47% (model 5.2) after adjusting for PS alone or both the PS and the 2 indications. In all models, the antidepressant exposure lost statistical significance ($P=0.30-0.39$), but no model fit the data significantly better than the reference model ($\chi^2=2.1, 4.3$; $df=1, 3$; $P>0.05$).

SEM analyses

Figure 1 represents the empirical SEM under our confounding by indication hypothesis ($\chi^2_M=16.3$, $df_M=11$, $P>0.05$; 90% CI of RMSEA: $0.0 - 0.06$; GFI: 0.996). Both depression-related diagnosis (unstandardized path coefficient: 0.38 , $P<0.05$; standardized: 0.43) and the CES-D score (0.02 , $P<0.05$; 0.17) were associated with increased antidepressant use. Based on the total standardized estimates, i.e., the sum of direct and indirect paths, a depression-related diagnosis and one additional depressive symptom, respectively, were expected to reduce HVLTL score by -0.073 and -0.034 standard deviations. The corresponding estimate for antidepressant exposure was -0.035 .

Assuming no indication bias (omitting the mediation paths 1 and 2 in Figure 1) resulted in a saturated model ($df_M=0$), whereas assuming maximum indication bias (eliminating the direct paths 3 and 4) appeared to be favorable ($\chi^2=3.2$, $df=2$, $P>0.05$). Removing the CES-D score from ($\chi^2=18$, $df=1$, $P<0.001$) or adding the CCI and hypertension severity to ($\chi^2=5.6$, $df=-2$, $P>0.05$) the mediation loop failed to reject the baseline model.

Sensitivity analyses

Sensitivity analyses derived consistent results. After adjusting for depression-related diagnosis and the CES-D score in MLR models (of the 4 comparison drug groups), the associations with sedatives (-0.34 ($P<0.05$) to -0.22 ($P=0.21$)) and antipsychotics (from -0.88 ($P<0.01$) to -0.59 ($P=0.13$)) diminished more than 30%; whereas the associations with antihypertensives (from -0.36 ($P=0.04$) to -0.30 ($P=0.08$)) and anticholinergics (-0.39 ($P<0.01$) to -0.31 ($P<0.05$)) decreased barely 20% or less. By redefining antidepressant exposure as *ever-never* (instead of “cumulative”) use in models 4.2 (MLR) and 5.2 (PS), the associations dropped 43.3% (-0.59 , $p=0.262$) and 40.6% (-0.62 , $p=0.241$) from the reference level (-1.04 , $p=0.021$), respectively. Refitting the PS-adjusted models using a new PS observed no further “bias” reduction (still -47%). Alternative SEMs assuming “reverse causality” ($\chi^2_M=53.6$, 67.3 , $df_M=12$, $P<0.001$) or “counterfactual” indications ($\chi^2_M=166.2$, $df_M=11$, $P<0.001$) fit the data poorly.

DISCUSSION

In this cohort of community-dwelling older men with hypertension, we demonstrated that the apparent association between antidepressant use and memory deficit diminished substantially and became non-significant after adjusting for potential indications for antidepressant prescribing, or a PS for it, but not by using the global comorbidity measures and other risk factors alone. In addition, the best fitting empirical SEM with greatest clinical interpretability seems the one under our *a priori* hypothesis of confounding by indications, which assumed antidepressant use to be a mediator between the indications and memory deficit, rather than an independent, primary “cause”. Further support was rendered from the sensitivity analyses. Ignoring potential cumulative antidepressant effects did not change the relationship. In addition, the impact of adjusting for depression was substantial on the associations for the two “antidepressant-spectrum” drug classes (i.e., benzodiazepines and antipsychotics), but was modest for other drug classes not intended for treating depression (i.e., antihypertensives and anticholinergics). Similarly, alternative SEMs assuming “reverse causality” or “counterfactual”-indications seem empirically implausible. These results suggest that the association between antidepressant use and memory impairment in older persons may reflect, at least in part, an indication bias of depression-related diagnoses and its symptom severity, which themselves have been associated with cognitive impairment (10–13, 34).

Among three analytic methods we explored, MLR and SEM appear comparable in terms of the magnitude of potential bias reduction on the estimated relationship (about 52%). However, SEM seems more didactically heuristic, conceptually intuitive and technically flexible to test the confounding by indication hypothesis. By explicitly specifying direct and indirect (or mediating), and feedback relationships in a model, SEM provides a unique empirical platform, on which competing causal hypotheses regarding the complex interrelationship for drug use, indications for prescribing and health outcomes can be quantitatively examined. However, the ever-growing model fit indices and the inconsistent use of such indices in current SEM literatures may have impeded its wider application to clinical and medical research (6–8, 33).

On the other hand, the PS method did not achieve anticipated gains in terms of validity (i.e., greater bias reduction) or efficiency (i.e., simpler hypothesis testing model). In fact, even “over-adjusting” the PS model for the source indication variables, the percent bias reduction was smaller than conventional MLR (47% versus 52%). We suspect there are two main reasons. First, the two depression-specific variables already provided sufficient information for quantifying indication bias; estimating a PS using these same variables (plus others) can not further improve model prediction. Second, when both the PS and its predictors, including the depression-specific variables, are adjusted in the same model, extra degrees of freedom are wasted and the probability of multi-collinearity increases. This observation is consistent with previous studies of PS modeling, either by direct covariate adjustment or by stratification (5, 35).

Our argument against antidepressant use as a potential cause of memory impairment was supported by findings from recent studies (12, 13, 15). Two pooled analyses of randomized

clinical trials in major depressive disorders demonstrated that successful antidepressant treatment with either tricyclic or SSRI agents improved, rather than compromised, patients' cognitive function (12, 13). Another observational study reported moderate improvement in global cognitive function associated with cumulative antidepressant use over twelve months in older medical patients with mild depression (15). Explanations include the resolution of mood disturbance attributed to therapeutic efficacy of the drugs, selective antidepressant prescribing devoid of harmful anticholinergic properties, and possible cognitive-enhancing property of some antidepressants (12–15). Whether or not these explanations apply to our findings is beyond the scope of this paper. The main message of our study is that using appropriate analytic methods to address potential confounding by disease-specific indications for drug prescribing is indeed a scientific necessity rather than statistical luxury to avoid erroneous causal claim from observational data of adverse drug events.

In conclusion, our study suggests that conventional MLR, PS and SEM are all capable of reducing indication bias in the estimated adverse associations between antidepressant use and memory performance. However, we found SEM approach preferable to its counterparts for several reasons. It is the only method that allows for explicit examination of competing causal hypotheses by specifying the directionality and hierarchy of assumed causal and non-causal relationships. Furthermore, it offers a rich set of model fit statistics to assist in model comparison. In observational studies of adverse drug effects on health outcome, an indication bias may be suggested when the following quantitative evidence emerge from testing alternative SEM under competing causal hypotheses (7, 8, 33):

1. A substantial (e.g., 40% or greater) reduction in the estimated association between the drug use and the health outcome after accounting for the clinically plausible indications for drug prescribing;
2. A statistically significant association ($p < 0.05$) between the indication(s) and the drug use (mediator) in clinically plausible direction, when other potential confounders are held constant;
3. A larger standardized estimate for the total indication “effect” on the health outcome including mediation via the drug use than that for the drug use, when other potential confounders are adequately controlled.

However, the above recommendations may be limited by the methodological constraints of this study, including the record-abstracted depression diagnosis, omission of dosage and duration of antidepressants and uncertainty about their actual use or adherence, and the broad grouping of concomitant medications. In addition, the unique nature of our study sample (i.e., male Veterans with hypertension under VA medical care and medication coverage) may limit the generalizeability of this study to older adults at large. Finally, to enhance conceptual clarity, we have focused on a single follow-up period and measured the outcome and PS only once. The principles and empirical procedures proposed here may need to be reevaluated using time-dependent propensity score, inverse-probability weighted marginal structural model and other more sophisticated technologies (36).

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Abbreviations used

CCI	Charlson comorbidity index
CES-D	Center for epidemiologic studies-depression scale
CFI	Comparative fit index
CI	Confidence interval
HVLT	Hopkins verbal learning test
MLR	Multiple linear regression
PS	Propensity score
RCT	Randomized clinical trial
RMSEA	Root mean squared error of approximation
SD	Standard deviations
SEM	Structural equation modeling
SSRIs	Selective serotonin reuptake inhibitors
VA	Veterans Administration

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Figure 1. Empirical SEM Delineating Potential Confounding By Indication in the Relationship Between Antidepressant Use and Memory Deficit Among 544 Hypertensive Older Men
Standardized path coefficients are provided. CESD, Center for Epidemiological Studies Depression Scale; HVLt, Hopkins Verbal Learning Test; D, Disturbance or proportion of unexplained variance of the endogenous variables by its presumed causes. For clarity sake, variance and covariance curves are omitted.

Table 1**Baseline Characteristics of 544 Older Hypertensive Men in the Study Cohort**

Characteristic	Value
Age, mean (SD)	74.4 (5.2)
White race, n (%)	483 (88.8)
Living alone before enrollment, n (%)	157 (29.1)
Education, years, mean (SD)	12.0 (2.8)
Current smoker, n (%)	447 (82.2)
Alcohol user (current or past), n (%)	283 (52.0)
Activity of daily living score, mean (SD) ^a	6.9 (0.4)
Chronic conditions, n (%) ^b	
<i>Cardiovascular diseases other than hypertension</i>	324 (59.6)
<i>Lung disease</i>	87 (16.0)
<i>Renal disease</i>	37 (6.8)
<i>Digestive diseases</i>	63 (11.6)
<i>Endocrine diseases</i>	192 (35.3)
<i>Tumors</i>	99 (18.2)
<i>Neurological, bone and joint diseases</i>	203 (37.3)
<i>All other conditions</i>	287 (52.8)
Charlson Comorbidity Index, mean (SD)	1.5 (1.4)
Moderate to severe hypertension, n (%) ^c	163 (30.0)
Blood pressure readings, mean (SD)	
<i>Systolic</i>	138.9 (18.7)
<i>Diastolic</i>	76.8 (10.3)
Depression and related psychiatric diagnoses (%) ^d	120 (22.1)
Center for Epidemiological Studies Depression Scale score, mean (SD) ^e	3.9 (3.7)
<u>Hopkins Verbal Learning Test</u> score, mean (SD) ^f	14.8 (4.5)
Medication use (%)	
<i>Antidepressants</i>	85 (15.6)
<i>Benzodiazepines/sedatives</i>	53 (9.7)
<i>Antipsychotics</i>	123 (22.6)
<i>Antihypertensives</i>	527 (96.9)
<i>Anticholinergics</i> ^g	342 (62.9)
Total number of medications used, mean (SD)	7.3 (3.3)

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

^aRange 0–7; higher scores indicate greater independence.

^bThese chronic conditions were used as individual binary predictors in the logistic regression model for estimating propensity score;

^cLevel 3 or 4 on a 4-level staging system by national guideline: 1 (normal, SBP<120 mmHg and DBP<80 mmHg), 2 (SBP 120–139 mmHg or DBP 80–89 mmHg), 3 (SBP 140–159 mmHg or DBP 90–99 mmHg) and 4 (SBP 160 mmHg or DBP 100 mmHg)

^dIncluded depression, posttraumatic stress disorders, anxiety and alcohol abuse or dependence, based on medical records.

^eRange 0–33; higher scores indicate greater symptomatic severity.

^fRange 0–36; higher scores indicate better memory.

^gBased on a clinician-rated anticholinergic score – 1 (range: 0–3), indicating at least mild anticholinergic potency.

Table 2

Association between Antidepressant Use and Memory Function Estimated Using Multiple Linear Regression Model Without Adjusting for Confounding by Indications

Model	Covariates adjusted	Antidepressant Use		
		Effect Estimate ^a	95% CI	P Value
1 ^b	None	-1.43	-2.62 – -0.24	0.018
2 ^c	Demographical and behavioral factors	-1.07	-2.02 – -0.13	0.026
3 ^d	Demographical, behavioral and comorbidity measures	-1.00	-1.94 – -0.06	0.038

Abbreviations: CI, confidence interval.

^a Represents the estimated decrement in the Hopkins Verbal Learning Test score associated with 1-unit increase in the cumulative antidepressant exposure.

^b Included the cumulative antidepressant use as a sole predictor.

^c Adjusted the cumulative antidepressant use for age, race, education, living alone before enrolment, activity of daily living score, tobacco and alcohol use, and baseline value of the Hopkins Verbal Learning Test score.

^d Adjusted for all the variables in Model 2, plus Charlson Comorbidity Index and severity of hypertension at baseline. This is the *reference model*, against which two different adjustment strategies for confounding by indication are to be examined (see Table 3).

Table 3

Association between Antidepressant Use and Memory Function Estimated Using Multiple Linear Regression Model Adjusting for Confounding by Indications

Model	Adjustment for Confounding By Indications ^a	Antidepressant Use		Comparison with Reference Model ^c	
		Effect Estimate ^b	95% CI	P-Value	Effect Estimate
4. Conventional model					
4.1	Depression-related diagnoses	-0.56	-1.64 – 0.52	0.311	-44.3%
4.2	Depression-related diagnoses and CESD score	-0.48	-1.58 – 0.62	0.389	-51.7%
5. Propensity-score model					
5.1	Propensity score	-0.58	-1.68 – 0.52	0.301	-41.9%
5.2	Propensity score, depression-related diagnoses and CESD score	-0.53	-1.63 – 0.58	0.347	-47.0%

Abbreviations: CI, confidence interval; CESD, Center for Epidemiological Studies Depression Scale.

^a Covariates are added to Model 3 of Table 2, included age, race, education, living alone before enrolment, activity of daily living score, tobacco and alcohol use, Charlson Comorbidity Index, severity of hypertension and Hopkins Verbal Learning Test score at baseline.

^b Represents the estimated decrement in the Hopkins Verbal Learning Test score associated with 1-unit increase in the cumulative antidepressant exposure.

^c Values represent differences on the effect estimates and maximum likelihood between each adjusted model and the *reference model* (Model 3 in Table 2).

-2LL gives the likelihood ratio χ^2 , with degree of freedom (df) equalling the number of additional parameters.