Original article

# Initiation of antidepressant medication and risk of incident stroke: using the Adult Changes in Thought cohort to address time-varying confounding

M. Maria Glymour, SD [a, *], Laura E. Gibbons, PhD [b], Paola Gilsanz, SD [c], Alden L. Gross, PhD, MHS [d], Jesse Mez, MD, MS [e], Paul W. Brewster, PhD [f], Jessica Marden, SD [g], Laura B. Zahodne, PhD [h], Kwangsik Nho, PhD [i], Jamie Hamilton, PhD [j], Gail Li, MD, PhD [k, l], Eric B. Larson, MD, MPH [b, m], Paul K. Crane, MD, MPH [b]

[a] Department of Epidemiology and Biostatistics, University of California, San Francisco, CA
[b] Department of Medicine, University of Washington, Seattle, WA
[c] Kaiser Permanente Division of Research, Oakland, CA
[d] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and Johns Hopkins University Center on Aging and Health, Baltimore, MD
[e] Alzheimer's Disease and Chronic Traumatic Encephalopathy Center, Boston University School of Medicine, Boston, MA
[f] Institute on Aging & Lifelong Health and Department of Psychology, University of Victoria, Victoria BC
[g] Analysis Group, Boston, MA
[h] Department of Psychology, University of Michigan, Ann Arbor, MI
[i] Center for Neuroimaging, Center for Computational Biology and Bioinformatics, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN
[j] The Michael J. Fox Foundation for Parkinson's Research, New York, NY
[k] Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA
[l] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA
[m] Kaiser Permanente Washington Health Research Institute, Seattle, WA

## ARTICLE INFO

## ABSTRACT

*Purpose:* Depression strongly predicts stroke incidence, suggesting that treating depression may reduce stroke risk. Antidepressant medications, however, may increase stroke risk via direct pathways. Previous evidence on antidepressant medication and stroke incidence is mixed. We evaluated associations between antidepressant use and incident stroke.
*Methods:* For 2302 Adult Changes in Thought cohort participants with no stroke at study entry, we characterized antidepressant use from pharmacy records, biennial depressive symptoms with a 10-item Centers for Epidemiologic Study—Depression scale, and incident strokes from ICD codes. We used discrete-time survival models with inverse probability weighting to compare stroke risk associated with filling antidepressant prescriptions and by medication category: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors, or other.
*Results:* Over an average 8.4-year follow-up, 441 incident strokes occurred. Filling antidepressant medications 3+ times versus 0—2 times predicted 35% increased odds of stroke (OR = 1.35; 95% CI: 0.98, 1.66). Use of TCAs was associated with stroke onset (OR per 10 fills = 1.28; CI: 1.04, 1.57), but use of selective serotonin reuptake inhibitors (OR = 0.98; CI: 0.80, 1.20) or other antidepressants (OR = 0.99; CI: 0.67, 1.45) was not.
*Conclusions:* Although patients who received antidepressant medication were at higher risk of stroke, this association appeared specific to TCA prescriptions.

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## Introduction

Depression in older adults is common and often undertreated [1]. Clinical depression and depressive symptoms strongly predict incidence of stroke [2, 3]; but it is not clear whether treating

* Corresponding author: 550 16th Street San Francisco, CA 94158. Tel.: +1 415 514 8140.
E-mail address: maria.glymour@ucsf.edu (M.M. Glymour).

depressive symptoms would reduce stroke risk. Depression may influence stroke incidence via deleterious health behaviors or stress-related mechanisms [4, 5]; but several previous studies reported that antidepressant medication use is associated with higher stroke incidence [2,6–9]. The association between antidepressant use and stroke has been observed for several antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and other antidepressants, but evidence has been inconsistent [6, 10, 11]. Elevated stroke risk among antidepressant users observed in previous studies may reflect the most severely depressed patients' increased likelihood of receiving antidepressant medications, rather than a harmful effect of the antidepressants themselves, that is, confounding by indication [12]. Teasing apart relationships between depression severity, antidepressant medication use, and stroke risk is important for clinical decision-making, especially in older adults who are at higher overall risk of stroke.

Addressing this question is challenging because depression severity is potentially both a confounder and a mediator of the relationship between antidepressant use and depressive symptoms (Fig. 1). Few data sets include both detailed history of antidepressant use and continuous measures of symptom severity; even when data are available, analytic methods to handle time-varying confounding are necessary [13, 14]. We used inverse probability weighting to estimate marginal structural models assessing the impact of antidepressant medication use on stroke risk in a cohort of older adults with linked information from surveys and pharmacy records.

## Methods

### Sample

The Adult Changes in Thought (ACT) cohort [15, 16] enrolled 3392 cognitively intact, community dwelling adults 65 years or older in two enrollment phases ($n = 2581$ in 1994–1996, $n = 811$ in 2000–2003), from a population-based integrated health care delivery system in King County, Washington (Group Health, now Kaiser Permanente Washington [KPW]). ACT initiated ongoing enrollments of 120–180 people per year in 2005. After obtaining informed consent, participants' demographic characteristics, medical history, and functional status were assessed using in-person biennial interviews. Each participant's study information was linked to KPW medical records and pharmacy files. For the current analyses, among 4131 consenting ACT participants with visits from inception (February 24, 1994) through data freeze (September 30, 2012), we excluded anyone with a baseline stroke (diagnosis or self-report) or self-reported transient ischemic attack ($n = 426$), and individuals who enrolled but had no follow-up ($n = 40$), leaving 3665 eligible participants. We further excluded any participants with a history of antidepressant medication from 1977 (the inception of electronic pharmacy records in KPW) to enrollment ($n = 1375$). Our final analytic sample included 2290

individuals followed up until first stroke, death, or end of administrative follow-up.

### Measures

Our outcome was first incident stroke, identified by ICD-9 codes included in the Center for Medicare and Medicaid Services' Chronic Condition Data Warehouse algorithm (430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02) extracted from inpatient and outpatient medical records. If the occasion with the putative stroke included any ICD codes associated with head injury (800–804.9 inclusive or 850 to 854.1 inclusive), or if the principal diagnosis for the billing occasion was V57.xx (rehabilitation services), then the occasion was not considered a stroke, even if other ICD codes would have qualified as a stroke (these include events such as traumatic brain injury). If the diagnosis was based on outpatient services, we required two stroke-related records within 12 months of each other to qualify the event as a stroke [17–19].

Our primary exposure, antidepressant medication use, including date of initiation and number of prescription fills, was extracted from KPW pharmacy records. Medications were categorized as any antidepressant, SSRI, TCA, or other antidepressant (see Appendix 1 for detailed medication listing). To avoid bias induced by individuals stopping antidepressants due to side effects or health concerns, our primary analyses focused on antidepressant initiation; this effectively categorized individuals as exposed to antidepressants for all time periods after their first prescription fill, even though many would have ceased using the medication.

We considered several alternative approaches to coding antidepressant medications to confirm results were robust. We created an indicator for having filled three or more prescriptions for primary analyses. We conducted sensitivity analyses in which we enforced a 1-month lag between the antidepressant use and incident stroke, by excluding all strokes that occurred in the same month that antidepressant medication was initiated. Anticipating a potential dose-response association between duration of antidepressant medication use and stroke risk, we also considered a linear term for number of prescriptions filled (effects expressed in units of 10 prescription fills).

All models were adjusted for time-constant covariates: sex, years of education, nonwhite race/ethnicity, and age in years at the baseline. We used inverse probability weighting (detailed in the following) to account for a set of covariates that were updated at each assessment wave. These variables were selected because they were plausible predictors of both initiation of antidepressants and stroke risk. These variables were extracted from medical records or survey responses. Depressive symptom severity was assessed with the continuous score on a 10-item Centers for Epidemiologic Studies–Depression (CES-D) scale [20]. Stroke risk was assessed with the components of the Framingham Stroke Risk Score, including type II diabetes mellitus diagnosis, current smoking,
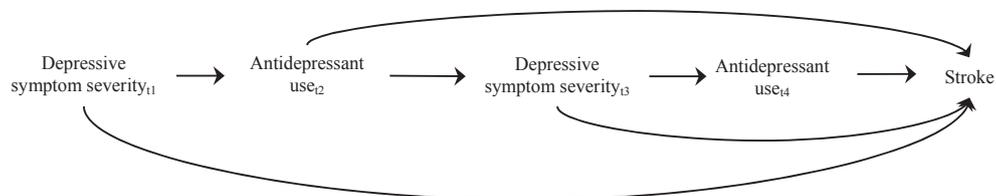


**Fig. 1.** Depressive symptom severity as a time-varying confounder that concurrently partially mediates the relationship between antidepressant use and stroke. Antidepressant use at time 2 (t2) is both influenced by previous depressive symptom severity (t1) and influences future depressive symptom severity (t3). Previous evidence indicates that depressive symptoms directly influence stroke risk, so depressive symptom severity both confounds and is a partial mediator for the effects of antidepressants.

systolic blood pressure, diagnoses of heart disease, atrial fibrillation, and left ventricular hypertrophy [21]. Additional time-updated covariates included marital status (married vs. all other), self-rated health (5-point scale from excellent to poor), limitations in Activities of Daily Living (count of self-reported limitations in six activities), self-report of exercise 15 + minutes 3 times per week or more, cognitive function based on the Cognitive Abilities Screening Instrument [22]; and body mass index (measured at clinic visits and self-reported at intervening assessments). We have monthly data on exposures and outcome, but many covariates were assessed only at biennial assessment waves; we carried forward the most recent past covariate values.

*Statistical analysis*

Marginal structural models are estimated by applying information from a model for the probability of treatment (antidepressant use) to an outcome model. We first evaluated the association of covariates, including depressive symptoms and other stroke risk factors, with the probability of initiating antidepressant medication use. These models were estimated defining each month of follow-up as a time interval and estimating odds of initiating antidepressants in that interval, censoring individuals after first antidepressant initiation [13]. We focus on the exposure of ever having initiated antidepressant medication, so respondents were considered exposed in all months after their first prescription fill (and the corresponding probability of subsequent exposures was 1 by definition because nobody who once initiated can ever reverse that status). We adopted a similar approach to account for selective attrition from the sample (estimating the probability the respondent remained in the sample), and the final weights were the product of confounding weights and attrition weights. We used stabilized weights, with the numerator equal to the estimated probability of receiving the treatment she/he received given time-constant covariates and the denominator estimated additionally including time-varying covariates [23].

We then estimated the outcome model, which was a discrete-time survival model for incident stroke with each outcome interval (i.e., each month during which a stroke might occur) reweighted based on the inverse of the probability the individual received the treatment he or she actually received in the previous month. Outcome models were estimated using a logit link in a weighted generalized linear regression model with sandwich variance estimators, in each month of observation and censoring after first recorded stroke. This model included a cubic spline to account for time since enrollment. Because stroke is rare, the logit model approximates a hazard. All time-constant variables used to estimate the numerators of the stabilized weights were included in the regression models.

For models of specific antidepressant class, the ideal model would reweight based on the probability of using the specific antidepressant, but these models did not converge, so we could only incorporate weights for use of any antidepressant.

We conducted several secondary analyses to assess the robustness of our findings. We estimated models restricting to individuals who ever had a depression diagnosis. Another set of models specified exposure as a count of prescriptions filled (in units of 10) and used this count to predict stroke in the overall sample and in analyses restricted to only those individuals with at least one antidepressant prescription fill. To rule out potential confounding due to individuals taking antidepressants for pain-related diagnoses, we repeated analyses excluding time at risk which accrued after any diagnosis related to pain (ICD codes: 307.81, 339.10–339.12, 339.42, 339.44, 339.89, 346.0–346.99, 355.9, 356.9, 729.2, 784.0). To evaluate the potential for bias due to the secular trend in the popularity of SSRIs, we tested whether estimated effects of antidepressant use differed before and after the year 2000.

To facilitate comparison with previous research [2,6–9]; we also estimated conventional models with or without adjustment for time-varying confounders, in which we did not apply weights.

## Results

Over an average of 8.4 years of follow-up, 441 incident first strokes were recorded (stroke rate = 2.2 per 100 person-years). At least one antidepressant prescription was filled during the follow-up period by 30% of the sample (Table 1). Predictors of initiation of antidepressant use included depressive symptoms (OR per additional depressive symptom = 1.07; 95% CI: 1.05, 1.10), female sex, lower education, worse self-reported health, more activities of daily living limitations, and worse cognitive function (Table 2).

Stroke incidence was nonsignificantly elevated in participants who initiated any antidepressant medication (OR = 1.23; 95% CI: 0.95, 1.62; Table 3), and those who filled three or more prescriptions (OR = 1.35; 95% CI: 0.98, 1.86). The odds of stroke incidence were estimated to increase by 8% per ten prescription fills (OR = 1.08; 95% CI: 0.93, 1.26), with CIs that included the null; results were identical in the full sample or when restricting to those with at least one prescription fill. Risk was significantly elevated when restricting to individuals who had a diagnosis of depression at some point during follow-up (OR = 1.84; 95% CI: 1.08, 3.14).

Focusing on the class of antidepressant, TCA use was significantly associated with stroke (OR = 1.28; 95% CI: 1.04, 1.57). Associations between stroke and SSRI use (OR = 0.98; 95% CI: 0.80, 1.20) or other antidepressants (HR = 0.99; 95% CI: 0.67, 1.45) were null.

We found little evidence that the associations differed in more recent periods of follow-up, with nonsignificant albeit positive (larger associations in later years) interactions of an indicator of follow-up after January 1, 2000, with both SSRI use (interaction b = .35, P = 0.56) and TCA use (interaction b = 1.27, P = 0.08). When excluding risk periods after pain-related diagnoses, results were similar (TCA HR per ten refills = 1.36; 95% CI: 1.10, 1.70; SSRI HR per ten refills = 1.01; 95% CI: 0.81, 1.25; other antidepressant HR per ten refills = 1.06; 95% CI: 0.67, 1.69).

## Discussion

In a large and well-characterized cohort of older adults, we confirmed the link between initiation of antidepressants and several risk factors previously documented to predict stroke. After accounting for these risk factors, including time-updated self-reported depressive symptoms, antidepressant use was associated with moderate increases in stroke risk, although the CIs were wide and included the null. When examining class of antidepressant medications, risk was significantly elevated only for TCAs, whereas risk associated with SSRIs was null. The absolute impact of the risk associated with TCA use would depend on the underlying incidence rate of stroke for each patient, but given an absolute stroke rate of 2.2 per 100 person years, an elevated risk of 28% would indicate 0.6 extra strokes per 100 person-years.

Our findings confirm the importance of accounting for depressive symptoms and other self-reported stroke risk factors when modeling associations of antidepressants with stroke risk. Depression and elevated depressive symptoms are robustly linked to stroke incidence, with meta-analyses suggesting a 34%–45% increase in stroke hazard [2, 3]. Depressed individuals are more likely to use antidepressant medications, with a 60% elevation a plausible lower bound (approximately as predicted by our models of antidepressant use assuming depressed people have a seven-point higher CES-D score than nondepressed). If

**Table 1**
Description of Adult Changes in thought cohort

| Characteristic | Full cohort | | Ever used an antidepressant | | Ever used a tricyclic[*] | | Ever used an SSRI[*] | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | mean/*n* | %/SD. | mean/*n* | %/SD. | mean/*n* | %/SD. | mean/*n* | %/SD. |
| Total | 2209 | 100% | 690 | 100% | 479 | 100% | 378 | 100% |
| Incident stroke cases | 441 | 19% | 128 | 19% | 95 | 20% | 80 | 21% |
| Years of follow-up | 8.4 | 5.5 | 10.9 | 5.1 | 10.8 | 5.2 | 11.0 | 4.9 |
| Baseline time-constant covariates | | | | | | | | |
| Male | 1105 | 48% | 267 | 39% | 190 | 40% | 135 | 36% |
| Years of education | 14.8 | 3.2 | 14.2 | 3.1 | 14.1 | 3.2 | 14.0 | 3.0 |
| Race other than white | 194 | 8% | 54 | 8% | 40 | 8% | 26 | 7% |
| Baseline values of time-varying covariates | | | | | | | | |
| Age | 74.3 | 6.3 | 74.9 | 6.2 | 74.6 | 6.2 | 75.2 | 5.9 |
| CES-D score (0–30) | 2.9 | 3.3 | 3.7 | 3.5 | 3.7 | 3.6 | 3.8 | 3.7 |
| Framingham stroke risk score | 8.6 | 7.4 | 8.4 | 7.1 | 8.2 | 6.7 | 8.4 | 7.0 |
| Diabetes | 205 | 9% | 63 | 9% | 44 | 9% | 32 | 7% |
| Smoking (current vs. all other) | 97 | 4% | 38 | 6% | 25 | 5% | 21 | 6% |
| Hypertension | 844 | 37% | 256 | 37% | 169 | 35% | 157 | 42% |
| Average systolic blood pressure | 140 | 21 | 141 | 21 | 141 | 21 | 143 | 21 |
| Heart disease | 374 | 16% | 117 | 17% | 80 | 17% | 66 | 18% |
| Atrial fibrillation | 169 | 7% | 37 | 5% | 26 | 5% | 19 | 5% |
| Left ventricular hypertrophy | 52 | 2% | 7 | 1% | 4 | 1% | 4 | 1% |
| Married or living as married | 1368 | 60% | 395 | 57% | 278 | 58% | 220 | 58% |
| Self-rated health (1 excellent - 5 poor) | 2.4 | 0.9 | 2.6 | 0.9 | 2.6 | 0.9 | 2.6 | 0.9 |
| Count of ADL limitations (0–6) | 0.2 | 0.7 | 0.3 | 0.7 | 0.3 | 0.7 | 0.3 | 0.6 |
| Cerebrovascular composite score (ever stroke, ever TIA, ever CEA) | 13 | 0% | 3 | 0% | 2 | 0% | 3 | 1% |
| Exercise regularly (15 + min at least 3x per wk) | 1673 | 73% | 495 | 72% | 347 | 73% | 266 | 71% |
| IRT CASI score (−4 to 1.75) | 0.35 | 0.7 | 0.28 | 0.71 | 0.29 | 0.73 | 0.26 | 0.69 |
| Body mass index | 27.2 | 4.8 | 27.2 | 4.8 | 27.3 | 4.9 | 27.3 | 4.6 |

ADL = activities of daily living; CEA = carotid endarterectomy; IRT CASI = Item Response Theory based Cognitive Assessment Screening Instrument; TIA = transient ischemic attack.
  [*] Some participants used both tricyclics and SSRIs.

depressed individuals also have a 40% elevation in stroke risk, this implies that simply because of confounding by indication, we would expect antidepressant users to have approximately a 24% higher risk of stroke than nonusers in analyses that did not account for symptoms. The actual bias is probably larger because factors such as cognitive functioning, which strongly predict stroke [24–26]; were also associated with initiating antidepressants, independently of CES-D score. Self-reported risk factors, such as self-rated health and activities of daily living limitations, rather than conditions associated with diagnosis codes, were the most salient predictors of antidepressant initiation. Such self-reported variables are rarely available in analyses based on administrative records.

Much previous work restricts analyses to individuals with a diagnosis of depression to reduce confounding by indication, but even among individuals with depression, severity of depression predicts initiation of and type of antidepressants. In the ACT cohort, each one point higher CES-D score was associated with a 5% higher odds of initiating antidepressant medication among individuals who ever received a diagnosis of depression. Thus, even when restricting to people who received a depression diagnosis, symptom severity may have confounded the association between antidepressant medication use and stroke risk. In analyses restricted to study participants with a diagnosis of major depression, the estimated effect of antidepressant use on stroke was more adverse than when estimated among the overall ACT sample. This suggests

**Table 2**
Predictors of antidepressant use in the Adult Changes in thought cohort

| Predictor | Baseline covariates | | | Baseline and time-dependent covariates | | |
| --- | --- | --- | --- | --- | --- | --- |
| | OR | 95% CI | | OR | 95% CI | |
| Female | 1.38 | 1.18 | 1.61 | 1.51 | 1.26 | 1.81 |
| Education (years) | 0.96 | 0.94 | 0.99 | 0.99 | 0.97 | 1.02 |
| White | 1.15 | 0.87 | 1.52 | 1.32 | 0.96 | 1.80 |
| Age | 1.03 | 1.02 | 1.05 | 1.01 | 0.99 | 1.02 |
| Cubic spline for time (months) | | | | | | |
| Intercept | 1.00 | 0.99 | 1.02 | 1.01 | 0.99 | 1.02 |
| Linear term | 0.92 | 0.76 | 1.13 | 0.89 | 0.73 | 1.09 |
| Quadratic term | 1.23 | 0.79 | 1.94 | 1.34 | 0.83 | 2.14 |
| Cubic term | 0.80 | 0.56 | 1.16 | 0.77 | 0.52 | 1.12 |
| Framingham stroke risk score | — | — | — | 1.00 | 0.99 | 1.01 |
| CES-D score | — | — | — | 1.07 | 1.05 | 1.10 |
| Married or live with partner | — | — | — | 1.05 | 0.88 | 1.25 |
| Self-rated health | — | — | — | 1.23 | 1.12 | 1.36 |
| ADL limitations | — | — | — | 1.11 | 1.02 | 1.22 |
| Cerebrovascular composite | — | — | — | 1.54 | 1.08 | 2.19 |
| Exercise regularly | — | — | — | 0.97 | 0.82 | 1.15 |
| IRT CASI score | — | — | — | 0.75 | 0.67 | 0.84 |
| Body mass index | — | — | — | 0.99 | 0.98 | 1.01 |

**Table 3**
Antidepressant use and incident stroke in the Adult Changes in thought cohort

| Characterization of antidepressant use | Conventional models, adjusted for baseline covariates | | | Conventional models, adjusted for baseline and time-dependent variables | | | Marginal structural models | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | HR | 95% CI | | HR | 95% CI | |
| Any use among full sample | | | | | | | | | |
| Never received antidepressant | 1.00 | — | — | 1.00 | — | — | 1.00 | — | — |
| At least one prescription | 1.14 | 0.92 | 1.41 | 0.97 | 0.76 | 1.23 | 1.23 | 0.95 | 1.62 |
| Filling 3+ prescriptions among full sample | | | | | | | | | |
| <=2 prescriptions | 1.00 | — | — | 1.00 | — | — | 1.00 | — | — |
| 3 + prescriptions | 1.36 | 1.05 | 1.76 | 1.21 | 0.90 | 1.61 | 1.35 | 0.98 | 1.86 |
| Any use among ever-diagnosed depressed | | | | | | | | | |
| Never received antidepressant | 1.00 | — | — | 1.00 | — | — | 1.00 | — | — |
| At least one prescription | 1.70 | 1.07 | 2.71 | 1.26 | 0.76 | 2.09 | 1.84 | 1.08 | 3.14 |
| Number of prescriptions filled among full sample | | | | | | | | | |
| Per ten refills | 1.06 | 0.99 | 1.15 | 1.03 | 0.93 | 1.14 | 1.08 | 0.93 | 1.26 |
| Number of prescriptions filled among people with at least one prescription | | | | | | | | | |
| Per ten refills | 1.11 | 1.02 | 1.20 | 1.03 | 1.01 | 1.26 | 1.08 | 0.93 | 1.26 |
| Type of medication among full sample | | | | | | | | | |
| No antidepressants | 1.00 | — | — | 1.00 | — | — | 1.00 | — | — |
| TCA | 1.16 | 1.03 | 1.31 | 1.18 | 1.02 | 1.38 | 1.28 | 1.04 | 1.57 |
| SSRI | 1.01 | 0.90 | 1.14 | 0.93 | 0.78 | 1.10 | 0.98 | 0.80 | 1.20 |
| Other medication | 0.98 | 0.68 | 1.43 | 1.08 | 0.74 | 1.56 | 0.99 | 0.67 | 1.45 |

that, surprisingly, restricting to individuals with depression may exacerbate confounding of the association between antidepressant use and risk of stroke. Antidepressant use in the absence of diagnosed depression appears common [27]. Patients who choose not to use antidepressant medication despite a diagnosis of major depression may be especially health-conscious or pursue other strategies to manage depression symptoms that have health benefits (e.g., increased physical activity). This may exacerbate the extent of confounding in analyses restricted to individuals with a diagnosis of depression.

Previous findings on the associations between antidepressant use and stroke risk are inconsistent, with the bulk of the evidence suggesting elevated stroke risk is associated with antidepressant use. A 2014 meta-analysis of studies of SSRI use and incident stroke identified only four previous cohort studies, with a pooled adjusted odds ratio of 2.12 (95% CI: 1.25–3.61) [8]. Few previous studies incorporate control for confounding by indication: among those four, only two included any control for depression severity [6, 7]; and an additional more recent cohort study included control for a binary indicator of depressive symptoms [9]. Combining our effect estimate of 0.98 with these three previous cohort studies gives an inverse-variance weighted effect estimate of 1.15 (95% CI: 1.02, 1.29) for the effect of SSRIs on risk for stroke. Thus, a best estimate incorporating both our findings and results from the handful of previous studies addressing confounding by indication is a small increase in stroke risk, although analyses that do not include control for a continuous symptom severity measure may have additional residual confounding. More evidence to provide greater precision and explain why effect estimates differ between cohorts would be valuable.

Previous evidence on TCAs and stroke is also inconsistent. Some studies suggest TCA users are at higher risk of stroke than either nonusers or SSRI users [11]; whereas others report TCA use has no association with stroke risk [7]. Inconsistent findings may partially reflect differences in practice patterns such that TCAs or SSRIs are systematically prescribed to individuals with more severe depression. Our results suggest a modest elevation in risk associated with TCA use.

The impact of antidepressants on stroke risk is of particular importance given recent interest in prescribing SSRIs to foster poststroke neurologic reorganization even in nondepressed stroke survivors [28–31]. Although we focus on first strokes, the mechanism via which antidepressants influence first stroke risk is likely relevant to recurrent stroke. The potential impact on recurrent stroke risk is important to evaluate if we are moving toward universal antidepressant treatment for stroke survivors, but will require a much larger sample to evaluate appropriately.

The ACT cohort is too small to support separate analyses of ischemic and hemorrhagic stroke. Previous work links SSRIs to hemorrhagic events, but effect sizes are so small they would likely be undetectable in ACT [32]. There is also limited evidence on the potential for depressive symptoms to confound associations between SSRI and hemorrhagic stroke [2]. Our results are from a highly educated and predominantly white sample. We know of no compelling evidence that biological effects of antidepressants on stroke risk differ by socioeconomic factors or race, but there is little research on effects of antidepressants in racial/ethnic minorities [33]. Our interpretation relies on the assumption of no unmeasured confounding, as in any observational study. Our control variables represent an unusually comprehensive list compared with other studies, but this assumption is unverifiable. One possible explanation for the elevated stroke risk associated with TCA use is that the CES-D does not adequately capture the depression severity that influences likelihood of TCA initiation. Because TCAs are often used as second line therapy for resistant depression, suggesting symptoms may be especially severe or persistent in TCA users, the possibility that CES-D does not capture depression severity that influences TCA initiation is a particular concern for estimates of the effects of TCA use. Similarly, the most recent CES-D score available from ACT study visits may not adequately capture the features of depression that predict stroke [34]. However, the association between the unobserved aspect of depression severity and likelihood of TCA use would have to be quite substantial to account for the observed association [35]. Regardless, our findings would ideally be confirmed using evidence from randomized trials.

Despite these limitations, our analyses make important advances in this important research area. To our knowledge, no previous study has implemented statistical analyses appropriate to control for confounding variables that may partially mediate the effects of antidepressants, as is the case with depressive symptoms [13, 14]. The design of ACT, integrating cohort-based assessments with administrative information from a large health care provider, provides an unusually rich set of covariates to control for confounding by indication.

The current findings from our study and others suggest little adverse effect of SSRIs on incident stroke risk. The evidence for TCAs is more worrisome, suggesting moderate excess stroke risk associated with using TCAs, although estimates for TCAs may also be more vulnerable to confounding, and TCAs, unlike SSRIs, are not currently recommended as poststroke prophylaxis. The results support the possibility of exploring nonpharmaceutical options to address depressive symptoms, although with persistent depression, the quality of life benefits of antidepressant pharmacotherapy may outweigh any adverse impacts on stroke risk. The specific findings that SSRIs had little associated stroke risk support the predominance of SSRIs as the preferred pharmaceutical therapy for depression [1, 36, 37].

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**Appendix. Medication categories**

*Tricyclics*

*Serotonin-2 antagonist/reuptake inhibitors (SARIs)*
    Nefazodone
    Trazodone.

*Tricyclic antidepressants & rel. Non-sel. Ru-inhib*
    Amitriptyline.
    Amoxapine
    Clomipramine.
    Desipramine.
    Doxepin.
    Imipramine.
    Maprotiline
    Nefazodone
    Nortriptyline.
    Protriptyline.
    Trazodone.

*SSRIs*

    Citalopram.
    Escitalopram.

    Fluoxetine.
    Fluvoxamine maleate.
    Paroxetine.
    Sertraline.

*Other antidepressants*

*Alpha-2 receptor antagonist antidepressants*
    Mirtazapine.

*Norepinephrine and dopamine reuptake inhib (NDRIS)*
    Bupropion.

*Serotonin-norepinephrine reuptake-inhib (SNRIS)*
    Duloxetine.
    Venlafaxine.

*Maois—nonselective and irreversible*
    Isocarboxazid.
    Marplan
    Tranylcypromine.