Research Article

Antidepressant Use Partially Mediates the Association Between Depression and Risk of Falls and Fall Injuries Among Older Adults

Matthew C. Lohman, PhD,^{1,*} Amanda J. Fairchild, PhD,² and Anwar T. Merchant, ScD, DMD¹

¹Department of Epidemiology and Biostatistics, University of South Carolina, Arnold School of Public Health, Columbia. ²Department of Psychology, University of South Carolina, Columbia.

*Address correspondence to: Matthew C. Lohman, PhD, Department of Epidemiology and Biostatistics, University of South Carolina, Arnold School of Public Health, Columbia, SC 29208. E-mail: lohmanm@mailbox.sc.edu

Received: August 26, 2020; Editorial Decision Date: September 27, 2020

Decision Editor: Anne B. Newman, MD, MPH, FGSA

Abstract

Background: The association between depression and fall risk in older adults is recognized, yet the mechanisms underlying this association are unclear. This study estimated the mediating role of antidepressant use in the association between depression and falls and fall injuries.

Methods: Longitudinal data from the Health and Retirement Study (2004–2006) were linked with medication data from the Prescription Drug Study (2005). The sample included community-dwelling adults aged ≥ 65 with data on depression and medication use ($n = 3565$). Depression was measured using 2 independent survey tools: Composite International Diagnostic Interview for depression short form and an 8-item version of the Center for Epidemiological Studies–Depression scale. We used causal mediation analysis to estimate and compare the direct and indirect (mediated by antidepressant use) effects of depression on falls and fall injuries.

Results: Individuals with major depressive disorder were significantly more likely to experience a fall (OR: 1.92; 95% CI: 1.41, 2.62) and a fall injury (OR: 1.67; 95% CI: 1.09, 2.55) over 2 years. Indirect effect estimates showed that antidepressant medication use accounted for approximately 19% and 18% of the association between major depressive disorder and falls and fall injuries, respectively. Results were similar when using an alternative depression measure and when considering only selective serotonin reuptake inhibitor antidepressants.

Conclusions: Antidepressant use explains a significant proportion, but not a majority, of the association between depression and greater fall risk. Treatment benefits of antidepressants should be considered with, and may outweigh, concerns about increased risk of falls associated with antidepressant use.

Keywords: Causal mediation analysis, Epidemiology, Falls and mobility problems

Falls are a salient and growing concern for older adults in the United States. Approximately 25% of adults aged 65 and older experience a fall each year (1), and while most do not result in serious injury, falls lead to approximately 2.8 million emergency department visits (2,3), 27 000 deaths (2), and over \$50 billion in medical costs annually (4). Further evidence indicates that rates of adverse fall-related injuries and mortality may also be increasing (5,6). Though the latter has led to proliferation of fall prevention programs, the use and effectiveness of these programs remain limited (7,8).

Major depressive disorder (MDD) is another common concern among older adults. Community prevalence estimates of MDD range from 1% to 5% (9–11), and fall risk is up to 4 times greater in this population, relative to older adults without MDD (12). An additional 15% of older adults present with clinically significant depressive symptoms (CSDS), while not meeting diagnostic criteria for MDD (13). Older adults with CSDS endorse more physiological symptoms as compared to younger adults (13–15), have a greater number of risk factors for falls such as greater frailty and functional

limitation (16,17), and are approximately 50% more likely to experience a fall than nondepressed counterparts (18). Despite consistent evidence of association between falls and both MDD and CSDS, the processes by which depression may cause or increase vulnerability to falls remain unclear.

Several potential explanations for the association between depression and falls have been proposed. First, various depressive symptoms such as cognitive changes, poor sleep, nutritional deficiency, and movement changes may directly predispose older adults to falls (18–21). Alternatively, the association may be explained by common risk factors such as chronic medical illness or functional disability (19,20). There may also be indirect, mediating factors underlying the association between depression and fall risk, such as antidepressant use, social isolation, or diminished physical activity. Although there has been little empirical evaluation of putative mediating mechanisms in the association of depression and falls, such knowledge may be especially important for identifying potential targets or methods for fall prevention or for helping clinicians avoid practices that could exacerbate fall risk.

Antidepressant use is common among older adults experiencing depressive symptoms, with approximately 19% reporting antidepressant use in the last month (22). Evidence suggests that older adults using antidepressants are more likely to fall than nonusers, independent of depression severity (20,23–26). Greater fall risk has been found for users of several antidepressant classes, including more commonly prescribed medications such as selective serotonin reuptake inhibitors (SSRIs) (24,27). Reflecting these findings, the Beers Criteria for potentially inappropriate medications among older adults recommends that clinicians avoid prescribing SSRIs, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors to those with history of fall or fracture (28). It remains unclear, however, to what degree such medications contribute to fall risk relative to other mechanisms or to depression itself. Such knowledge would help to determine whether antidepressant avoidance is warranted when weighed against their effectiveness in treating depression.

In light of previous research, the primary aims of this study were (i) to estimate the direct effects of MDD and CSDS on falls and fall-related injuries in the United States, and (ii) to estimate the indirect effects of MDD and CSDS on falls through antidepressant use, using a potential outcomes-based causal mediation approach. Based on prior research, we hypothesized that depression would be associated with elevated risk of both falls and fall-related injuries and that a significant proportion of the association would be mediated by use of antidepressant medications.

Method

Data and Sample

This study used data from 2 large-scale data sources: the Health and Retirement Study (HRS) and the Prescription Drug Study (PDS) (29,30). The HRS is an ongoing, nationally representative survey regarding health and financial characteristics of adults aged 51 and older in the United States, supported by funding from the National Institute on Aging (grant number NIA U01AG009740). The HRS core survey is conducted biennially by phone with a cohort of approximately 20 000 new and continuing participants in each wave. Health and Retirement Study employs a multistage sampling design to obtain a representative sample of noninstitutionalized adults in the United States. Core survey respondents report on an

extensive set of socioeconomic, demographic, and health-related variables (31).

Medication data were drawn from the PDS, a 2-wave mail survey designed to track changes in prescription drug use among HRS respondents from 2005 to 2007. The PDS sample was drawn from 2004 HRS core survey respondents who were 63 or older in 2005 or covered by Medicare or Medicaid in the previous 2 years ($n = 5654$ eligible participants). Prescription Drug Study participants reported on a range of medication-related variables, including prescription drug use, costs, coverage, and satisfaction. Medication data from respondents to the initial 2005 PDS survey were linked with the HRS core survey for the present analysis.

The analytic sample for the present study included HRS respondents aged 65 and older who participated in 2 core survey waves in 2004 and 2006 and who responded to the PDS survey ($n = 3776$). We additionally excluded participants who responded by proxy or resided in a nursing home at baseline ($n = 95$) and those missing data on depression or fall occurrence ($n = 116$), yielding an analytic sample of 3565. More details regarding eligibility and selection are shown in [Supplementary Figure 1](#).

Measures

Outcomes

At each wave, HRS core survey respondents aged 65 and older were asked to report occurrence of falls since the previous interview. Respondents who reported any fall were asked to report the number of falls and whether any of those falls caused injury requiring medical treatment during that period. For the present analysis, we considered falls or fall-related injuries reported during the 2006 HRS wave as binary (yes/no) outcomes.

Exposure

Depression was measured in 2 ways, to differentiate formal depression diagnoses versus presentation of clinically significant symptoms. First, during baseline interviews, HRS respondents completed the Composite International Diagnostic Interview for depression short form (CIDI-SF). The CIDI-SF is a brief screening tool for estimating the 12-month prevalence of major depressive episodes (32,33) based on the full CIDI (34), a measure found to have moderate diagnostic accuracy for MDD compared to clinical interview (Kappa = 0.53) (35). Respondents who reported at least 1 of 2 screening criteria—depressed mood or loss of interest in normally pleasurable activities—for most/all of the day almost every day during a 2-week period, were asked to report presence or absence of 6 other symptoms (33). In accordance with Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) guidelines (36), respondents who endorsed 5 or more symptoms were considered to have experienced MDD (32,37). Second, scores from the 8-item version of the Center for Epidemiological Studies-Depression (CES-D) scale were considered as a continuous measure of depressive symptom severity not exclusive to an MDD diagnosis. The CES-D asks respondents to report presence of 8 depressive symptoms during the previous 2 weeks and is administered in each HRS wave. We considered a score of 3 or greater on the CES-D as indicative of CSDS, in line with previous validation studies (37).

Mediator

Data regarding antidepressant and other prescription medications come from the baseline PDS (2005) interview. Respondents were asked to report all currently prescribed medications. Because

frequency, dosage, and adherence were not reported in a systematic or standardized manner, we considered those who reported any current prescription as current users. We considered several classes of antidepressant medications individually and in aggregate, including SSRIs, TCAs, monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants. Medications within each class were identified by generic or brand name (see [Supplementary Table 1](#) for specific names). Other prescription medications considered in analysis, including opiates, benzodiazepines, and other anxiolytic medications, were identified using similar methods ([Supplementary Table 1](#)).

Covariates

Several sociodemographic and health-related covariates were considered in analyses as potential confounders based on prior research. Continuous covariates included age (years), education (years), comorbidity burden (sum of 8 chronic conditions), and functional limitations (sum of 5 activities of daily living [ADL] limitations). Categorical covariates included gender, use of anxiolytic medication or opiates, race (indicator variables for White, Black, other), smoking history (indicator variables for current, former, never). Covariates were included in analytic models based on previous research and an empirical confounder selection method described below.

Analysis

We calculated frequencies of falls, fall-related injuries, antidepressant medication use, and demographic characteristics by depression status and compared distributions using *t* tests and chi-square tests for continuous and categorical variables, respectively.

The primary study aims were evaluated using causal mediation analysis, a potential outcome (counterfactual)-based extension of traditional mediation modeling that is flexible to different statistical models of the outcome and presence of exposure–mediator interaction (38–41). The procedure makes use of counterfactual estimates for each observation to estimate average causal effects of the exposure, yielding both direct and indirect effects at all possible values of the mediator variable. We implemented mediation models using the Stata package “paramed” to decompose effects of depression on fall risk into direct effects and indirect effects mediated by antidepressant use. We estimated the natural direct effects (NDE), natural indirect effects (NIE), total effect (TE), and proportion of effect mediated (PEM) on the odds ratio scale (42), using logistic regression conditioned on selected confounders. We fit independent models for each of the outcomes—falls and fall-related injuries—and each metric of the exposure—MDD and CSDS. To assess potential interaction effects between the exposure (depression) and mediator (antidepressant use), we estimated each model both with and without inclusion of an exposure–mediator interaction. Model covariate selection was guided by previous literature and directed acyclic graphs ([Figure 1](#)). We additionally evaluated potential confounding using an empirical change-in-estimate procedure: First, we fit an unadjusted logistic regression model estimating the association between exposure (MDD) and outcome (falls). Covariates were added to the model sequentially and variables producing a greater than 5% change from the crude association were retained for adjustment. This process was repeated for assessing exposure–mediator and mediator–outcome confounding.

All analyses were performed using Stata statistical software (version 14.1; StataCorp LP, College Station, TX).

Sensitivity Analyses

We performed sensitivity analyses to evaluate the robustness of model results to potential violations of causal mediation analysis assumptions. First, to gauge the potential effects of unmeasured confounding, we estimated causal mediation models under different unobserved confounding scenarios—none, moderate, and strong—corresponding to the degree of association between a hypothetical unmeasured confounder and the outcome (43,44). Second, we used the “gformula” package in Stata to estimate mediation models in the presence of a mediation–outcome confounder affected by exposure—anxiolytic medication use ([Supplementary Figure 1](#)).

Results

Summary statistics for participant sociodemographic and health characteristics by depression classification are presented in [Table 1](#). In the analytic sample, 190 (5.3%) respondents met criteria for MDD and 514 (14.4%) met criteria for CSDS at baseline. Although presence of MDD and CSDS at baseline were significantly related ($\chi^2 = 124.7, p < .01$), a minority ($n = 80, 42.1\%$) of respondents with MDD also had CSDS. Older adults with MDD were notably younger than those without MDD and significantly more likely to be female, a current smoker, to have at least one ADL limitation, and to use an antidepressant in 2005. We found similar differences between those with and without CSDS ([Table 1](#)). Approximately 11% of respondents reported use of an antidepressant in 2005, with SSRIs (71.9%) and TCAs (19.4%) the most common classes. Those with MDD and CSDS were significantly more likely to report a fall or fall-related injury than nondepressed counterparts.

Mediation Analyses

Model estimates for MDD as the exposure are shown in [Table 2](#). Comparison of model estimates and tests of statistical significance suggested no significant exposure–mediator interaction ($p_{\text{interaction}} = .882$); therefore, only model estimates assuming no exposure–mediator interaction are presented. Results from models allowing for exposure–mediator interaction were similar and substantively equivalent to the primary analyses ([Supplementary Tables 2 and 3](#)). After adjusting for key potential exposure–outcome, exposure–mediator, and mediator–outcome confounders, we estimated that individuals with MDD were approximately twice as likely to report a fall ($OR_{TE}: 1.92, 95\% CI: 1.412, 2.621$) and 86.4% more likely to report a fall-related injury ($OR_{TE}: 1.864,$

Figure 1. Conceptual diagram of causal mediation analyses. ADL = activities of daily living.

Table 1. Demographic and Health Characteristics of Analytic Sample by Baseline MDD and CSDS Classification ($n = 3565$)

	Total	MDD	No MDD		CSDS	No CSDS	
	3565	190	3375		514	3051	
	<i>N</i> (%) or <i>M</i> (<i>SD</i>)	<i>N</i> (%) or <i>M</i> (<i>SD</i>)	<i>N</i> (%) or <i>M</i> (<i>SD</i>)	<i>p</i> Value	<i>N</i> (%) or <i>M</i> (<i>SD</i>)	<i>N</i> (%) or <i>M</i> (<i>SD</i>)	<i>p</i> Value
Sociodemographic							
Age, <i>y</i> (mean, <i>SD</i>)	75.39 (7.78)	72.66 (7.05)	75.55 (7.79)	<.001	75.62 (7.74)	74.97 (7.50)	.071
Female	2185 (61.29)	140 (73.68)	2045 (60.59)	<.001	370 (71.98)	1815 (59.49)	<.001
Race				.394			<.001
White	2962 (83.09)	152 (80.00)	2810 (83.26)		390 (75.88)	2572 (84.30)	
Black	483 (13.55)	32 (16.84)	451 (13.36)		99 (19.26)	384 (12.59)	
Other	120 (3.37)	6 (3.16)	114 (3.38)		25 (4.86)	95 (3.11)	
Years education (mean, <i>SD</i>)	11.87 (3.38)	10.97 (3.58)	11.92 (3.36)	<.001	10.56 (3.56)	12.22 (3.21)	<.001
Health							
Smoking status				<.001			<.001
Never	1609 (45.43)	80 (42.33)	1529 (45.60)		207 (40.51)	1401 (46.26)	
Former	1614 (45.57)	77 (40.74)	1537 (45.84)		231 (45.21)	1368 (45.13)	
Current	319 (9.01)	32 (16.93)	287 (8.56)		73 (14.29)	261 (8.61)	
≥1 Chronic condition	692 (19.41)	49 (20.53)	653 (19.35)	.326	116 (22.57)	563 (18.59)	.218
≥1 ADL limitation	829 (23.25)	70 (36.84)	759 (22.49)	<.001	209 (40.66)	511 (15.01)	<.001
Used anxiolytic or sedative	229 (6.42)	22 (11.58)	207 (6.13)	.003	63 (12.26)	206 (6.75)	<.001
Used opiate	294 (8.52)	24 (12.63)	270 (8.00)	.024	66 (12.84)	222 (7.28)	<.001
Mediator/outcome							
Used antidepressants	391 (10.97)	36 (18.95)	355 (10.52)	<.001	95 (18.48)	296 (9.70)	<.001
SSRI	281 (7.88)	24 (12.63)	257 (7.61)		71 (13.81)	210 (6.88)	
TCA	76 (2.13)	5 (2.63)	71 (2.10)		16 (3.11)	60 (1.97)	
Other	38 (1.07)	7 (3.68)	31 (0.92)		11 (2.14)	27 (0.88)	
Reported fall	1224 (34.33)	85 (44.74)	1139 (33.75)	.002	249 (48.44)	975 (31.96)	<.001
Reported fall injury	393 (11.02)	30 (15.79)	363 (10.76)	.031	89 (17.32)	304 (9.96)	<.001

Notes: ADL = activities of daily living; CSDS = clinically significant depressive symptoms; MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

95% CI: 1.221, 2.847). Use of any antidepressant medication was a significant mediator of the association between MDD and falls (OR_{NIE} : 1.133, 95% CI: 1.091, 1.177) and fall-related injuries (OR_{NIE} : 1.117, 95% CI: 1.068, 1.169), equating to 19.1% and 17.8% of the total effects being mediated, respectively. Results were similar when the mediating effect of only SSRIs was considered, with SSRI medication accounting for approximately 10% of the total effect of MDD on falls and fall-related injuries. We did not find evidence of an indirect effect on falls or fall-related injuries through TCA use.

Table 3 displays models estimates considering CSDS as primary exposure. As with MDD, respondents with CSDS had significantly greater likelihood of reporting falls (OR_{TE} : 2.166, 95% CI: 1.780, 1.635) and fall-related injuries (OR_{TE} : 1.918, 95% CI: 1.466, 2.510), compared to those without CSDS. Likewise, there were significant indirect effects indicating that the relationship between CSDS and both falls (OR_{NIE} : 1.131, 95% CI: 1.088, 1.175) and fall-related injuries (OR_{NIE} : 1.105, 95% CI: 1.056, 1.157) were mediated by antidepressant use, accounting for 15.9% and 15.4% of the total effect of CSDS, respectively. There was a significant indirect effect of only SSRIs for both outcomes (Falls OR_{NIE} : 1.103, 95% CI: 1.062, 1.146; Fall-related injuries OR_{NIE} : 1.080, 95% CI: 1.035, 1.127), but we did not find a statistically significant indirect effect through TCA use on falls or fall-related injuries.

Sensitivity Analyses

Table 4 presents model estimates under different scenarios of hypothetical unmeasured confounding. Assuming moderate unmeasured

confounding ($OR_U = 1.5$), the direct and indirect effects of MDD on falls were only slightly diminished ($OR_{NDE} = 1.621$; $OR_{NIE} = 1.125$) with 18.1% of fall likelihood mediated by antidepressant use, with no change in inference. Results were similar when modeling fall-related injuries as the model outcome. Likewise, estimates of direct and indirect effects of CSDS on falls and fall-related injuries were only slightly diminished in the moderate unmeasured confounding condition (Table 4), with no change in inference. In the strong unmeasured confounding scenario ($OR_U = 5.0$), effect estimates for both MDD and CSDS were diminished to a greater degree but remained substantively consistent with the primary analysis. Major depressive disorder and CSDS were associated with between 29.8% and 48.9% greater odds of falls or fall-related injuries directly. Further, antidepressant use still accounted for between 9.8% and 13.4% of the total effect of MDD and CSDS on fall outcomes. In a separate sensitivity analysis, we reestimated models under the condition of a mediator–outcome confounder (anxiolytic medication use) affected by depression (Supplementary Figure 2). Although estimates were diminished as compared to the primary analysis, both direct effects of MDD and CSDS on falls and indirect effects through antidepressant use remained statistically significant and substantively similar to the primary findings (Supplementary Table 4).

Discussion

In this large cohort of community-dwelling older adults, we found that 2 measures of depression, MDD and CSDS, were each associated with significantly greater risk of experiencing falls and

Table 2. Direct and Indirect Effects of Major Depressive Disorder (MDD) on Falls and Fall-Related Injuries in Analytic Sample ($n = 3565$)

	Falls					Fall Injuries				
Mediator		OR	95% CI		<i>p</i> Value		OR	95% CI		<i>p</i> Value
Any AD										
Med	NDE	1.698	1.248	2.311	.001	NDE	1.669	1.093	2.548	.018
	NIE	1.133	1.091	1.177	<.001	NIE	1.117	1.068	1.169	<.001
	TE	1.924	1.412	2.621	<.001	TE	1.864	1.221	2.847	.004
	PEM*	0.191				PEM*	0.178			
SSRI	NDE	1.745	1.284	2.370	<.001	NDE	1.720	1.128	2.621	.012
	NIE	1.068	1.040	1.097	<.001	NIE	1.062	1.030	1.095	<.001
	TE	1.864	1.371	2.534	<.001	TE	1.827	1.198	2.785	.005
	PEM*	0.106				PEM*	0.100			
TCA	NDE	1.810	1.336	2.454	<.001	NDE	1.784	1.174	2.711	.007
	NIE	1.010	1.000	1.021	.060	NIE	1.006	0.994	1.019	.328
	TE	1.829	1.349	2.480	<.001	TE	1.795	1.181	2.728	.006
	PEM*	0.017				PEM*	0.011			

Notes: AD = antidepressant medication; NDE = natural direct effect; NIE = natural indirect effect; OR = odds ratio; PEM = percent effect mediated; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TE = total effect. All models were adjusted for age, race, gender, limitations in activities of daily living, and anxiolytic medication use.

*PEM calculated on log odds scale: $\log \text{NIE}/\log \text{TE}$.

Table 3. Direct and Indirect Effects of Clinically Significant Depressive Symptoms (CSDS) on Falls and Fall-Related Injuries in Analytic Sample ($n = 3565$)

		Falls				Fall Injuries				
Mediator		OR	95% CI		<i>p</i> Value		OR	95% CI		<i>p</i> Value
Any AD										
Med	NDE	1.915	1.576	2.327	<.001	NDE	1.736	1.327	2.270	<.001
	NIE	1.131	1.088	1.175	<.001	NIE	1.105	1.056	1.157	<.001
	TE	2.166	1.780	2.635	<.001	TE	1.918	1.466	2.510	<.001
	PEM*	0.159				PEM*	0.154			
SSRI	NDE	1.941	1.598	2.356	<.001	NDE	1.758	1.344	2.298	<.001
	NIE	1.103	1.062	1.146	<.001	NIE	1.080	1.035	1.127	<.001
	TE	2.141	1.760	2.603	<.001	TE	1.898	1.452	2.481	<.001
	PEM*	0.129				PEM*	0.120			
TCAs	NDE	2.031	1.676	2.462	<.001	NDE	1.838	1.408	2.399	<.001
	NIE	1.007	0.998	1.016	.118	NIE	1.005	0.995	1.015	.330
	TE	2.045	1.688	2.479	<.001	TE	1.846	1.414	2.410	<.001
	PEM*	0.010				PEM*	0.008			

Notes: AD = antidepressant medication; NDE = natural direct effect; NIE = natural indirect effect; OR = odds ratio; PEM = percent effect mediated; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TE = total effect. All models were adjusted for age, race, gender, limitations in activities of daily living, and anxiolytic medication use.

*PEM calculated on log odds scale: $\log \text{NIE}/\log \text{TE}$.

fall-related injuries over 2 years. Results further suggest that antidepressant use is a significant mediator of these associations, accounting for between 16% and 19% of the total effect of depression on falls. Findings were consistent across multiple outcomes, with antidepressant use accounting for between 15% and 18% of the association between fall-related injuries and CSDS and MDD, respectively. While several explanations for the association between depression and falls have been proposed, the present findings provide a quantitative basis with which to compare the relative importance and strength of alternative direct and indirect mechanisms.

Our finding that antidepressant use mediates the association between depression and fall risk is consistent with, and extends, previous research. Several cross-sectional and prospective studies have noted the independent associations of depression and antidepressants with fall risk (12,18,21,23,26,27). Notably, a prospective

study by Quach et al found a 67% greater incidence of falls among individuals with CSDS that the authors suggested was partially mediated by antidepressant use, although the size and significance of the indirect effect were not evaluated (23). In the present study, a statistically significant proportion of the association between depression and fall outcomes was mediated by general antidepressant use. Several observational studies have also found associations between specific antidepressant classes and fall risk. For instance, a meta-analysis by Gebara et al found that 17 of 26 observational studies indicated a positive association between SSRI use and falls (27), and subsequent pooling of study data suggested 66% greater odds of falls among those taking SSRIs (45). Indeed, the present results support the hypothesis that SSRI use may increase fall risk independent of depression severity. Although we did not find similar evidence of an indirect role of TCAs or other antidepressant classes, these results

Table 4. Sensitivity of Effect Estimates to Strength of Association Between an Unmeasured Confounder (U) and the Outcome

	No Unmeasured Confounding (observed analysis)			Moderate Unmeasured Confounding (OR _U = 1.5)*			Strong Unmeasured Confounding (OR _U = 5.0)*		
	OR _{NDE}	OR _{NIE}	PEM	OR _{NDE}	OR _{NIE}	PEM	OR _{NDE}	OR _{NIE}	PEM
A. Major depressive disorder (MDD)									
Falls	1.698	1.133	0.191	1.621	1.125	0.181	1.321	1.092	0.134
Fall injuries	1.669	1.117	0.178	1.593	1.110	0.168	1.298	1.078	0.120
B. Clinically significant depressive symptoms (CSDS)									
Falls	1.915	1.131	0.159	1.828	1.122	0.149	1.489	1.088	0.109
Fall injuries	1.736	1.105	0.154	1.657	1.097	0.143	1.350	1.066	0.098

Notes: AD = antidepressant medication; NDE = natural direct effect; NIE = natural indirect effect; OR = odds ratio; PEM = percent effect mediated; TE = total effect.

*Estimates assume hypothetical prevalence of U within strata of exposure/mediator: P(No MDD/No AD) = 10%; P(MDD/No AD) = 20%; P(No MDD/AD) = 20%.

should be interpreted with caution, as few sample respondents used antidepressants other than SSRIs.

The present results help update several potential explanations for the associations between depression, antidepressants, and falls. First, research suggests that the symptoms and correlates of depression, such as sleep disturbances, appetite and nutritional changes, fatigue, and trouble concentrating, may play a key role in increasing risk for falls (18–21). The consistency of estimates for both a survey diagnostic measure of major depression (MDD) and a broader measure of depressive symptoms (CSDS) lends support to this idea. Furthermore, although we found that antidepressants may explain a significant proportion of the association, most of the greater fall likelihood (>80%) was due to direct effects, attributable to either the symptoms of depression or to other mediating pathways not considered in the present analysis. A second explanation for the association between depression and falls is the influence of common causes. For instance, individuals with greater functional limitation and chronic disease comorbidity are more likely to experience falls and to report a greater number of depressive symptoms (9,20,46). Clinical severity of depression and other conditions may in turn influence the prescription of antidepressant medications. While the present analyses adjusted for key health and demographic confounders determined through an empirical selection process, it is possible that confounding from unmeasured common causes biased estimates. Nevertheless, our sensitivity analyses indicated that results were robust to relatively strong unmeasured confounding, suggesting that unmeasured common causes of depression, falls, and antidepressant use, if present, could not fully explain the estimated associations. Lastly, the present results lend support to the hypothesis that depression influences fall risk through indirect pathways such as antidepressant use. As others have suggested, antidepressants may increase fall risk through hypotensive effects (23), by increasing physical activity and exposure to falling (23), dizziness (47), or other unknown mechanisms. The relative strength and significance of other potential mediating pathways, such as sarcopenia, frailty, and social isolation, were beyond the scope of this study and are left to future research to evaluate.

Strengths of this study include use of longitudinal data from a population-based sample and causal mediation analysis. The comprehensive data allowed for consideration of multiple measures of depression and focus on specific types of antidepressant use in relation to multiple fall outcomes. In addition, sensitivity analyses helped gauge the potential impact of violations of certain causal

mediation assumptions, strengthening confidence in the robustness of estimates.

This study has several limitations that should be considered. First, antidepressant frequency and dosage information were unavailable, so it is unclear how these factors may have influenced estimates. Second, research suggests that self-reported falls may be subject to poor recall, leading to underreporting of fall events (48). Nevertheless, we found similar associations when analyzing fall-related injuries, which are less likely to be forgotten or underreported. Third, presence of comorbidities like Parkinson's disease, which may confound studied associations, was unknown; however, sensitivity analyses suggested that estimates were robust to moderate and strong unmeasured confounding. Fourth, measures of depression at the time of antidepressant use (2005) were unavailable. Depression severity in 2005 may have influenced both the prescription of antidepressants and likelihood of subsequent falls. This may therefore represent a violation of the causal mediation assumption of no mediator–outcome confounder affected by exposure if depression severity changed substantially from baseline to 2005. Although our sensitivity analyses suggested that estimates were robust to this type of violation, we were unable to assess all similar violations.

The results of this study have implications for fall prevention and depression treatment among older adults. Current Beers Criteria guidelines indicate that antidepressants such as SSRIs may be inappropriate for older adults with a history of falling (28). Although the present results further substantiate the indirect role of antidepressants in the association between depression and fall risk, they also indicate that depressive symptoms or mechanisms other than antidepressants may play an even greater role in determining risk of falling. This suggests that the therapeutic effects of antidepressants in reducing depressive symptoms (and thus fall risk) should be considered in clinical evaluation and may potentially outweigh any increase in risk of falls associated with antidepressants. Evidence suggests that antidepressants are as effective in treating depression among older adults as younger adults (14,49). These findings may also inform fall prevention. While many prevention approaches focus on physiological factors to determine who is at risk and how to intervene against falls (7,50), the present results add to growing evidence that psychological and social factors play an important role in risk of falls and injuries, independent of physical health characteristics. The consistency and strength of associations found in this and other studies indicate that incorporating psychological factors like depression into screening tools may improve their accuracy

and expand the population of older adults eligible for preventive interventions.

In summary, this study is among the first attempts to disentangle direct and indirect effects of depression on fall risk among older adults. The results provide quantitative evidence that antidepressant use plays a significant mediating role in this association, but that the direct effects of depression or other intermediate factors may play an even greater role in increasing fall risk. Such information is important for individuals weighing the benefits of pharmacologic treatment for depression with potential side effects. Future research quantifying and comparing the magnitude of alternative intermediate mechanisms such as sarcopenia, frailty, and social isolation is warranted.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This work was supported by a grant from the National Institute on Aging at the National Institutes of Health (grant number R21AG064310).

Conflict of Interest

None declared.

Acknowledgments

Data used for this study are available from the Health and Retirement Study (HRS) at <https://hrs.isr.umich.edu/data-products>. Access to sensitive data from the Prescription Drug Study used in this study is available from HRS under a Sensitive Data Access Use Agreement and therefore cannot be shared by the authors.

Author Contributions

M.C.L. contributed to the conception of the study, the analysis and interpretation of data, and the drafting and revision of the manuscript. A.J.F. contributed to the analysis and interpretation of data and the drafting and revision of the manuscript. A.T.M. contributed to the analysis and interpretation of data and the drafting and revision of the manuscript.

References

- Bergen G, Stevens MR, Burns ER. Falls and fall injuries among adults aged ≥ 65 years—United States, 2014. *Morb Mortal Wkly Rep*. 2016;65(37):993–998. doi:10.15585/mmwr.mm6537a2
- Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. 2005. www.cdc.gov/injury/wisqars. Accessed March 1, 2020.
- Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. *Am J Public Health*. 1992;82:1020–1023. doi:10.2105/ajph.82.7.1020
- Florence CS, Bergen G, Atherly A, Burns E, Stevens J, Drake C. Medical costs of fatal and nonfatal falls in older adults. *J Am Geriatr Soc*. 2018;66(4):693–698. doi:10.1111/jgs.15304
- Hartholt KA, Polinder S, Van Beeck F, et al. End of the spectacular decrease in fall-related mortality rate: men are catching up. *Am J Public Health*. 2012;102(suppl 2):S207–S211. doi:10.2105/AJPH.2011.300288
- Hartholt KA, Lee R, Burns ER, Van Beeck EF. Mortality from falls among US adults aged 75 years or older, 2000–2016. *JAMA*. 2019;321(21):2131–2133. doi:10.1001/jama.2019.4185
- Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to prevent falls in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;319(16):1705–1716. doi:10.1001/jama.2017.21962
- Hopewell S, Adedire O, Copsey BJ, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2018;7:CD012221. doi:10.1002/14651858.CD012221.pub2
- Blazer D. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):249–265. doi:10.1093/gerona/58.3.m249
- Hybels CF, Blazer DG. Epidemiology of late-life mental disorders. *Clin Geriatr Med*. 2003;19(4):663–696. doi:10.1016/s0749-0690(03)00042-9
- Bruce ML, McAvay GJ, Raue PJ, et al. Major depression in elderly home health care patients. *Am J Psychiatry*. 2002;159(8):1367–1374. doi:10.1176/appi.ajp.159.8.1367
- Stubbs B, Stubbs J, Gnanaraj SD, Soundy A. Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. *Int Psychogeriatr*. 2016;28(1):23–29. doi:10.1017/S104161021500126X
- Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annu Rev Clin Psychol*. 2009;5(1):363–389. doi:10.1146/annurev.clinpsy.032408.153621
- Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365(9475):1961–1970. doi:10.1016/S0140-6736(05)66665-2
- Beekman A, Deeg D, Van Tilburg T, Smit J, Hooijer C, Van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord*. 1995;36(1–2):65. doi:10.1016/0165-0327(95)00061-5
- Lohman M, Dumenci L, Mezuk B. Depression and frailty in late life: evidence for a common vulnerability. *J Gerontol B Psychol Sci Soc Sci*. 2016;71(4):630–640. doi:10.1093/geronb/gbu180
- Lohman MC, Mezuk B, Dumenci L. Depression and frailty: concurrent risks for adverse health outcomes. *Aging Ment Health*. 2017;21(4):399–408. doi:10.1080/13607863.2015.1102199
- Kvelde T, McVeigh C, Toson B, et al. Depressive symptomatology as a risk factor for falls in older people: systematic review and meta-analysis. *J Am Geriatr Soc*. 2013;61(5):694–706. doi:10.1111/jgs.12209
- Iaboni A, Banez C, Lam R, et al. Depression and outcome of fear of falling in a falls prevention program. *Am J Geriatr Psychiatry*. 2015;23(10):1088–1097. doi:10.1016/j.jagp.2015.02.006
- Iaboni A, Flint AJ. The complex interplay of depression and falls in older adults: a clinical review. *Am J Geriatr Psychiatry*. 2013;21(5):484–492. doi:10.1016/j.jagp.2013.01.008
- Kvelde T, Pijnappels M, Delbaere K, Close JC, Lord SR. Physiological and cognitive mediators for the association between self-reported depressed mood and impaired choice stepping reaction time in older people. *J Gerontol A Biol Sci Med Sci*. 2010;65:538–544. doi:10.1093/gerona/glp195
- Pratt LA, Brody DJ, Gu Q. *Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014*. Hyattsville, MD: National Center for Health Statistics; 2017.
- Quach L, Yang FM, Berry SD, et al. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. *J Gerontol A Biol Sci Med Sci*. 2013;68(12):1575–1581. doi:10.1093/gerona/glt084
- Naples JG, Kotlarczyk MP, Perera S, Greenspan SL, Hanlon JT. Non-tricyclic and non-selective serotonin reuptake inhibitor antidepressants and recurrent falls in frail older women. *Am J Geriatr Psychiatry*. 2016;24(12):1221–1227. doi:10.1016/j.jagp.2016.08.008
- Macri JC, Iaboni A, Kirkham JG, et al. Association between antidepressants and fall-related injuries among long-term care residents. *Am J Geriatr Psychiatry*. 2017;25(12):1326–1336. doi:10.1016/j.jagp.2017.08.014
- Kerse N, Flicker L, Pfaff JJ, et al. Falls, depression and antidepressants in later life: a large primary care appraisal. *PLoS One*. 2008;3(6):e2423. doi:10.1371/journal.pone.0002423

27. Gebara MA, Lipsey KL, Karp JF, Nash MC, Iaboni A, Lenze EJ. Cause or effect? Selective serotonin reuptake inhibitors and falls in older adults: a systematic review. *Am J Geriatr Psychiatry*. 2015;23(10):1016–1028. doi:[10.1016/j.jagp.2014.11.004](https://doi.org/10.1016/j.jagp.2014.11.004)
28. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:[10.1111/jgs.15767](https://doi.org/10.1111/jgs.15767)
29. Health and Retirement Study. *Rand Longitudinal File Public Use Dataset*. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI: University of Michigan; 2016.
30. Health and Retirement Study. *Prescription Drug Study (PDS) 2005 (Final V1.0)*. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI: University of Michigan; 2008.
31. Wallace RB, Herzog AR. Overview of the health measures in the health and retirement study. *J Hum Resour*. 1995;30:S84. doi:[10.2307/146279](https://doi.org/10.2307/146279)
32. Steffick DE. *Documentation of Affective Functioning Measures in the Health and Retirement Study*. Vol DR-005. Ann Arbor, MI: Survey Research Center; 2000.
33. Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen HU. The World Health Organization composite international diagnostic interview short-form (CIDI-SF). *Int J Methods Psychiatr Res*. 1998;7(4):171–185. doi:[10.1002/mpr.47](https://doi.org/10.1002/mpr.47)
34. Kessler RC, Abelson J, Demler O, et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). *Int J Methods Psychiatr Res*. 2004;13(2):122–139. doi:[10.1002/mpr.169](https://doi.org/10.1002/mpr.169)
35. Kessler RC, Wittchen HU, Abelson JM, et al. Methodological studies of the composite international diagnostic interview (CIDI) in the US national comorbidity survey (NCS). *Int J Methods Psychiatr Res*. 1998;7(1):33–55. doi:[10.1002/mpr.33](https://doi.org/10.1002/mpr.33)
36. American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Arlington, VA: American Psychiatric Association (APA); 1980.
37. Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. *Int Psychogeriatr*. 1999;11(2):139–148. doi:[10.1017/s1041610299005694](https://doi.org/10.1017/s1041610299005694)
38. VanderWeele TJ. Explanation in causal inference: developments in mediation and interaction. *Int J Epidemiol*. 2016;45(6):1904–1908. doi:[10.1093/ije/dyw277](https://doi.org/10.1093/ije/dyw277)
39. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health*. 2016;37(1):17–32. doi:[10.1146/annurev-publhealth-032315-021402](https://doi.org/10.1146/annurev-publhealth-032315-021402)
40. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18(2):137–150. doi:[10.1037/a0031034](https://doi.org/10.1037/a0031034)
41. Valeri L, Vanderweele TJ. The estimation of direct and indirect causal effects in the presence of misclassified binary mediator. *Biostatistics*. 2014;15(3):498–512. doi:[10.1093/biostatistics/kxu007](https://doi.org/10.1093/biostatistics/kxu007)
42. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010;172(12):1339–1348. doi:[10.1093/aje/kwq332](https://doi.org/10.1093/aje/kwq332)
43. VanderWeele TJ. Bias formulas for sensitivity analysis for direct and indirect effects. *Epidemiology*. 2010;21(4):540–551. doi:[10.1097/EDE.0b013e3181df191c](https://doi.org/10.1097/EDE.0b013e3181df191c)
44. Ding P, Vanderweele TJ. Sharp sensitivity bounds for mediation under unmeasured mediator-outcome confounding. *Biometrika*. 2016;103(2):483–490. doi:[10.1093/biomet/asw012](https://doi.org/10.1093/biomet/asw012)
45. Stubbs B. A meta-analysis investigating falls in older adults taking selective serotonin reuptake inhibitors confirms an association but by no means implies causation. *Am J Geriatr Psychiatry*. 2015;23(10):1098. doi:[10.1016/j.jagp.2015.02.004](https://doi.org/10.1016/j.jagp.2015.02.004)
46. Kao S, Wang YC, Tzeng YM, Liang CK, Lin FG. Interactive effect between depression and chronic medical conditions on fall risk in community-dwelling elders. *Int Psychogeriatr*. 2012;24(9):1409–1418. doi:[10.1017/S1041610212000646](https://doi.org/10.1017/S1041610212000646)
47. Joe E, Forester B. Strategies to manage antidepressant adverse effects in the elderly. *Psychiatr Times*. 2010.
48. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *J Am Geriatr Soc*. 2005;53(12):2190–2194. doi:[10.1111/j.1532-5415.2005.00509.x](https://doi.org/10.1111/j.1532-5415.2005.00509.x)
49. Kok RM, Reynolds CF 3rd. Management of depression in older adults: a review. *JAMA*. 2017;317(20):2114–2122. doi:[10.1001/jama.2017.5706](https://doi.org/10.1001/jama.2017.5706)
50. Park SH. Tools for assessing fall risk in the elderly: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2018;30(1):1–16. doi:[10.1007/s40520-017-0749-0](https://doi.org/10.1007/s40520-017-0749-0)