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Association of Antidepressants With Recurrent, Injurious and Unexplained Falls is Not Explained by Reduced Gait Speed

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ABSTRACT

Objective: *To examine if antidepressants at baseline are associated with falls and syncope over 4 years follow-up and if any observed associations are explained by baseline gait speed.* ***Design:*** *Longitudinal study (three waves).* ***Setting:*** *The Irish Longitudinal Study on Ageing (TILDA), a nationally representative cohort study.* ***Participants:*** *Two thousand ninety-three community-dwelling adults aged ≥60 years.* ***Measurements:*** *Antidepressants (ATC code "N06A") were identified. Recurrent falls (≥2 falls), injurious falls (requiring medical attention), unexplained falls, and syncope were reported at either Wave 2 or 3. Usual gait speed was the mean of two walks on a 4.88 m GAITRite walkway. Poisson regression analysis was used to examine associations between baseline antidepressant use and future falls adjusting for sociodemographics, physical, cognitive and mental health, and finally, gait speed.* ***Results:*** *Compared to non-antidepressant users, those on antidepressants at baseline were more likely to report all types of falls (24.8–40.7% versus 9.8–18%) at follow-up. Antidepressants at baseline were independently associated with injurious falls (incidence risk ratio: 1.58, 95% confidence interval: 1.21, 2.06, $z = 3.38$, $p = 0.001$, $df = 32$) and unexplained falls (incidence risk ratio: 1.49, 95% confidence interval: 1.04, 2.15, $z = 2.17$, $p = 0.030$, $df = 32$) independent of all covariates including gait speed.* ***Conclusion:*** *There was little evidence to support the hypothesis that gait would (partly) explain any observed associations between baseline use of antidepressants and future falls. The underlying mechanisms of the observed relationships may be related*

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to depression, vascular pathology, or direct effects of antidepressants. Clinicians should identify the best treatment option for an individual based on existing risk factors for outcomes such as falls. (Am J Geriatr Psychiatry 2020; 28:274–284)

OBJECTIVE

Prescription of antidepressants is common among older adults, not just in the treatment of depression but also anxiety, panic disorder, neuropathic pain, and urinary incontinence.[1] Based on a Eurobarometer survey carried out in 27 European countries, 9.5% of adults aged 55 and over reported antidepressant use in the past year[2] while Mars et al.[3] showed that antidepressant prescribing in the United Kingdom increased between 1995 and 2011, particularly in adults aged 46 and over. In older adults, antidepressant use has been associated with an increased likelihood of adverse outcomes such as cardiovascular events, hyponatremia, falls, and fractures possibly due to an increase in co-morbidities, polypharmacy, and age-related pharmacokinetic and pharmacodynamic changes.[4]

Existing literature has reported associations between antidepressant use and recurrent falls in both cross-sectional[5,6] and longitudinal analysis.[7,8] Antidepressants have also been cross-sectionally associated with injurious falls[5] and syncope[9] while longitudinal associations have been reported for antidepressants with single falls[10] and combined recurrent/injurious falls.[11]

It is currently unclear if falls are due to the underlying depression or if antidepressants enhance the risk further or change the mechanism of risk.[1] Several meta-analysis and review articles have concluded that depression or depressive symptoms in older adults are associated with an increased risk of falls.[12,13] However, we previously demonstrated that antidepressants, but not depressive symptoms, are associated with reduced usual gait speed.[14] This simple measure provides insight into an individual's functional capacity and research has shown that reduced gait speed is independently associated with a number of adverse outcomes including increased risk of future falls.[15]

The complexity of this relationship is not fully understood, however it is possible that an observed relationship between antidepressants and falls may be explained to some extent by slow usual gait speed. In this study, we firstly examine if antidepressant use at baseline is a significant predictor of recurrent, injurious, and unexplained falls and syncope occurring in community-dwelling adults aged 60 and older over 4 years follow-up. Secondly, we examine if any relationships are explained by baseline usual gait speed.

METHODS

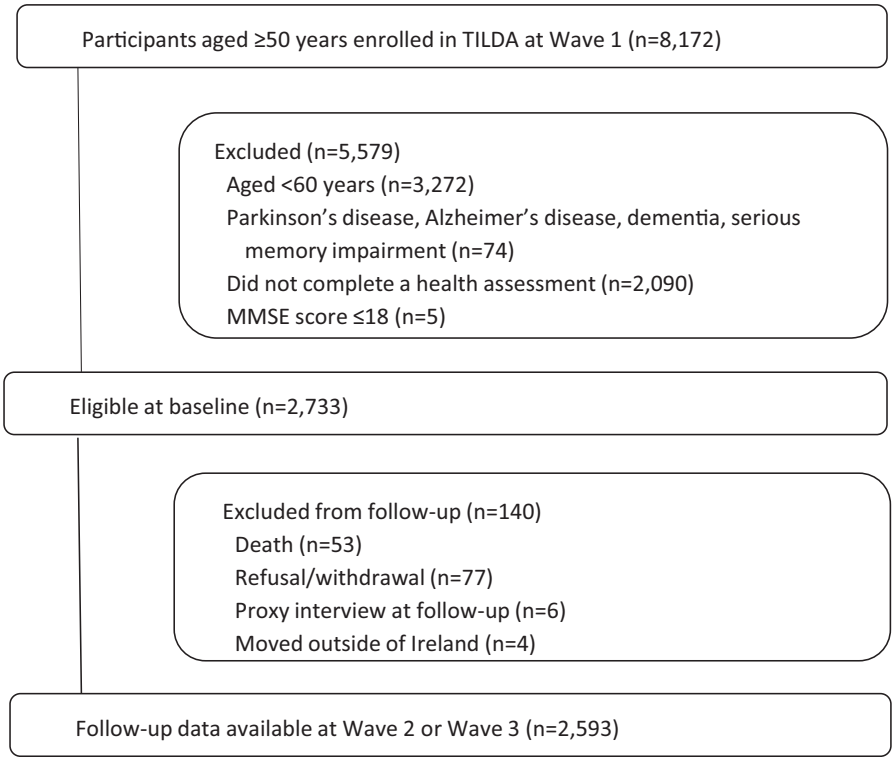
Study Design

The Irish Longitudinal Study on Ageing (TILDA) is a large-scale prospective study of the social, economic, and health circumstances of community-dwelling adults in Ireland. The sampling frame is the Irish Geodirectory, a listing of all residential addresses in the Republic of Ireland. A clustered sample of addresses was chosen, and household residents aged 50 years and older and their spouses/partners (of any age) were eligible to participate. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and written informed consent was obtained from all participants. Study design and details of the cohort have been described in detail previously.[16]

Data Collection

Data collection involved 1) a computer-assisted personal interview that included detailed questions on socio-demographics, wealth, health, lifestyle, social support and participation, use of health and social care, and attitudes to ageing, 2) a self-completion questionnaire, which contained more sensitive information, and 3) a comprehensive health assessment carried out by research nurses. Baseline data from 8,174 participants aged 50 and older were obtained between January 2009 and July 2011 with follow-up interview data obtained at Wave 2 (February 2012–March 2013) or Wave 3 (March 2014

FIGURE 1. Exclusion criteria used to establish eligible participants for this analysis.
Note: MMSE: Mini-Mental State Examination; TILDA: The Irish Longitudinal Study on Ageing.



−October 2015). Inclusion criteria for this analysis was baseline age greater than or equal to 60 years, Mini-Mental State Examination (MMSE) score greater than 18, no self-reported doctor diagnosis of Parkinson's disease or cognitive impairment, and participation in a health center assessment (n = 2,733); details of the participants included are provided in the flowchart in Figure 1.

Falls Outcome Variables

A number of dichotomous falls variables were derived at each wave. Recurrent falls were defined as two or more falls occurring in the past year or since the last interview. In the literature, injurious falls are defined in a number of different ways e.g., some include all bruises, grazes while some require emergency department attendance. Here, injurious falls were defined if a participant reported that they had injured themselves seriously enough to require medical attention. Unexplained falls were identified as non-accidental falls i.e., those in which there was no apparent or obvious reason for the fall. Syncope was also reported in the past year.

Antidepressants

Medications were coded using the World Health Organisation's Anatomical Therapeutic Chemical (ATC) codes and antidepressants were identified as any medications beginning with "N06A." Antidepressant use at baseline was used as the predictor variable in the analysis.

Other Covariates

A number of covariates were obtained during the interview. Sociodemographic variables such as age, sex, living status (living alone or living with others), and educational level (primary, secondary, or tertiary

corresponding to ≤8, 9−13, or ≥14 years of education) were obtained. Depressive symptoms were assessed using the 20-item Centre for Epidemiological Studies Depression (CES-D) scale (maximum score 60).[17] The number of self-reported doctor diagnosed cardiovascular conditions was obtained from the following list: angina, heart attack, heart failure, stroke or mini-stroke, heart murmur, and heart arrhythmia. Self-reported history of osteoarthritis, urinary incontinence, and moderate/severe chronic pain was also recorded. The following medications that increase fall risk were identified: antihypertensives (ATC codes: C02, C03, C07, C08, C09), antipsychotics (ATC code: N05A), benzodiazepines (ATC codes: N05BA, N05CD or N05AE), and benzodiazepine-related drugs (ATC code: N05CF); the number of categories of fall-increasing medications that a participant was taking was used in the analysis. Smoking history was obtained and participants were classified as being a non-smoker, previous smoker or current smoker while problem drinking was assessed using the CAGE questionnaire.[18] Participants were asked if they were afraid of falling with answers categorized as no, somewhat or very much afraid. Finally, participants rated their steadiness when walking as very steady, slightly steady, slightly unsteady, and very unsteady[19] with unsteadiness defined as any response other than very steady.

During the health assessment, participants were asked to walk at their usual pace along a computerized GAITRite mat with embedded pressure sensors (4.88 m active area). They started 2.5 m before the mat and finished 2 m after the mat to allow for acceleration and deceleration. Usual gait speed was calculated as the average speed obtained from two walks. Global cognition was assessed using the MMSE[20] while the choice reaction time test used a computer based program to assess concentration and processing speed. Participants depressed a button on a specially designed keyboard and waited for a stimulus (yes/no) to appear on the screen. In response, the participants pressed the corresponding yes/no button on the keyboard. Total reaction time was the time from when the stimulus was displayed until the corresponding yes/no button was pressed.

Beat-to-beat blood pressure was measured during an active stand procedure as outlined previously.[21] Participants rested supine for 10 minutes, following which they were asked to stand in a timely manner. Systolic and diastolic blood pressure was recorded for 2 minutes after standing. Orthostatic hypotension was defined as a drop in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg, 30 seconds after standing.

Visual acuity was assessed using an Early Treatment Diabetic Retinopathy Study logMAR chart (Precision Vision, La Salle, IL) at a viewing distance of 4 m and using habitual distance vision correction if required. The best acuity value from either eye was converted to a Visual Acuity Score where higher values indicate better acuity. A quantitative heel bone ultrasound (Achilles Heel Ultrasound, Lunar, Madison, WI) was used to assess bone health and the risk of osteoporotic fracture. This device provides an index of bone stiffness and while this is not diagnostic, an individual is considered to have osteoporosis, osteopenia, or normal bone density if the stiffness index is less than 65%, 65−86% or higher than 86%, respectively.[22]

Statistical Analysis

Statistical analysis was conducted using Stata v14 (StataCorp LP, TX). All analyses were weighted with respect to age, sex, and education to the 2011 Census to ensure that data were nationally representative. Data were further weighted by health status and sociodemographic factors to account for participants who did not attend a health center assessment.

Baseline characteristics were obtained for adults who were and were not on antidepressants. We used generalized linear models with poisson regression and robust estimates to examine the association between antidepressants and falls (recurrent, injurious, and unexplained) and syncope occurring over 4 years follow-up. Model 1 was unadjusted; Model 2 adjusted for age, sex, education, height, weight, living status, number of cardiovascular conditions, osteoarthritis, chronic pain, urinary incontinence, heel bone stiffness, number of categories of medications with increased fall risk, fall history (if relevant), fear of falling, unsteadiness while walking, smoking status, depressive symptoms at baseline (i.e., CES-D score), MMSE, total choice reaction time, grip strength, visual acuity, orthostatic hypotension, and duration of follow-up. Finally, Model 3 additionally adjusted for usual gait speed.

Complete covariate data for Model 3 was available for 92.1% of participants. Complete case analysis was

TABLE 1. Characteristics for Adults Who are and are Not Taking Antidepressants at Baseline

	Not on Antidepressants (n = 2,448)	On Antidepressants (n = 145)	Total (n = 2,593)
Age (years), mean (SD)	67.8 (6.1)	67.5 (6.0)	67.8 (6.1)
Sex (female), n (%)	1305 (53.3)	92 (63.45	1397 (53.9)
Education, n (%)			
Primary	691 (28.2)	55 (37.9)	746 (28.8)
Secondary	928 (37.9)	46 (31.7)	974 (37.6)
Tertiary	828 (33.8)	44 (30.3)	872 (33.6)
Height (m), mean (SD)	1.65 (0.09)	1.64 (0.09)	1.65 (0.09)
Weight (kg), mean (SD)	78.4 (15.4)	78.6 (18.9)	78.4 (15.6)
Lives alone, n (%)	506 (20.7)	99 (68.3)	552 (21.3)
MMSE, mean (SD)	28.5 (1.6)	28.2 (1.7)	28.5 (1.6)
Total reaction time (ms), mean (SD)	853 (290)	931 (305)	857 (291)
Cardiovascular conditions, n (%)			
0 conditions	1888 (77.1)	86 (59.3)	1974 (76.1)
1 condition	394 (16.1)	41 (28.3)	435 (16.8)
2 conditions	123 (5.0)	12 (8.3)	135 (5.2)
≥3 conditions	43 (1.8)	6 (4.1)	49 (1.9)
Osteoarthritis, n (%)	435 (17.8)	38 (26.2)	473 (18.2)
Urinary incontinence, n (%)	331 (13.6)	42 (29.2)	373 (14.4)
Moderate/severe pain, n (%)	597 (24.4)	70 (48.3)	667 (25.8)
Heel bone stiffness, n (%)			
Normal	1067 (43.9)	61 (42.4)	1128 (43.8)
Risk of osteopenia	1082 (44.5)	68 (47.2)	1150 (44.6)
Risk of osteoporosis	284 (11.7)	15 (10.4)	299 (11.6)
Depressive symptoms, mean (SD)	4.6 (5.8)	9.6 (9.6)	4.9 (6.1)
Grip strength (kg), mean (SD)	25.1 (9.3)	22.2 (8.5)	25.0 (9.3)
Visual acuity (VAS), mean (SD)	95.4 (9.3)	94.9 (9.5)	95.3 (9.3)
Orthostatic hypotension, n (%)	446 (18.2)	41 (28.3)	487 (18.8)
Unsteadiness while walking, n (%)	448 (18.3)	50 (34.5)	498 (19.2)
Fall history, n (%)			
0 falls	1927 (78.7)	93 (64.1)	2020 (77.9)
1 fall	357 (14.6)	27 (18.6)	384 (14.8)
≥2 falls	163 (6.7)	25 (17.2)	188 (7.3)
Fear of falling, n (%)			
No fear of falling	1865 (76.2)	86 (59.3)	1951 (75.3)
Somewhat afraid	470 (19.2)	46 (31.7)	516 (19.9)
Very afraid	112 (4.6)	13 (9.0)	125 (4.8)
Smoking status, n(%)			
Never	1,156 (47.2)	58 (40.0)	1214 (46.8)
Past	1025 (41.9)	63 (43.4)	1088 (42.0)
Current	267 (10.9)	24 (16.6)	291 (11.2)
Problem drinking (CAGE)	211 (9.4)	28 (20.4)	239 (10.0)
Number of high fall risk medications, mean (SD)	0.5 (0.6)	0.9 (0.7)	0.5 (0.6)
Usual gait speed (m/s), mean (SD)	1.31 (0.20)	1.21 (0.22)	1.31 (0.20)
Follow-up (years), mean (SD)	4.2 (0.7)	4.3 (0.6)	4.2 (0.7)

Notes: Data are weighted and presented as Mean (SD) for continuous variables; number (%) for categorical variables. CAGE = Cut, Annoyed, Guilty, Eye-opener; MMSE = Mini-Mental State Examination; VAS = Visual Analog Scale.

used for multivariate analyses i.e., all missing data were treated as missing at random. We then repeated this analysis, excluding those with a history of falls in the past year. Significance level was set at $p<0.05$.

RESULTS

In this population based sample of older adults (mean age: 68 years; range: 60–93 years; 53.9% female), 7.0% of participants (n = 180) reported potentially clinically relevant depressive symptoms while 5.6% of participants (n = 145) were taking antidepressants at baseline, irrespective of their depressive symptoms score. Baseline characteristics of participants stratified by antidepressant use at baseline are provided in Table 1. Older adults on antidepressants were more likely to be female, living alone, smokers, to report more cardiovascular conditions, osteoarthritis, moderate/severe pain, medications with a high

TABLE 2. Prevalence of Falls Occurring After 4 Years Follow-up in Those Taking and not Taking Antidepressants at Baseline

	On Antidepressants N (%)	Not on Antidepressants N (%)	Total N (%)
Recurrent falls	58 (40.0)	441 (18.0)	499 (19.2)
Injurious falls	59 (40.7)	440 (18.0)	499 (19.2)
Unexplained falls	36 (24.8)	241 (9.8)	277 (10.7)
Syncope	7 (4.8)	110 (4.5)	117 (4.5)

TABLE 3. Bivariate and Multivariate Associations between Antidepressants at Baseline and Fall Outcomes in Those with and without A History of Falls

Including Those With a History of Falls

	Recurrent Falls IRR (95% CI), z-Value, p Value	Injurious Falls IRR (95% CI)	Unexplained Falls IRR (95% CI)	Syncope IRR (95% CI)
Model 1	1.93 [1.49, 2.49], 4.97, p <0.001	1.96 [1.52, 2.54], 5.15, p <0.001	2.49 [1.76, 3.53], 5.15, p <0.001	1.30 [0.57, 2.99], 0.62, p = 0.536
Model 2	1.37 [1.05, 1.80], 2.29, p = 0.022	1.64 [1.27 2.12] 3.78, p <0.001	1.61 [1.13, 2.29], 2.63, p = 0.009	1.40 [0.63, 3.12], 0.82, p = 0.414
Model 3	1.31 [0.99, 1.74], 1.92, p = 0.055	1.58 [1.21, 2.06], 3.38, p = 0.001	1.49 [1.04, 2.15], 2.17, p = 0.030	1.36 [0.61, 3.05], 0.76, p = 0.449
N	2389-2593	2389-2593	2389-2593	2389-2593

Excluding Those With a History of Falls

	Recurrent Falls IRR (95% CI)	Injurious Falls IRR (95% CI)	Unexplained Falls IRR (95% CI)	Syncope IRR (95% CI)
Model 1	1.60 [1.04, 2.45], 2.15, p = 0.031	1.50 [1.00, 2.24], 1.95, p = 0.052	2.57 [1.57, 4.21], 3.74, p <0.001	2.21 [0.94, 5.24], 1.81, p = 0.070
Model 2	1.49 [1.00, 2.23], 1.98, p = 0.048	1.46 [0.98, 2.16], 1.88, p = 0.060	1.67 [1.09, 2.57], 2.36, p = 0.018	2.26 [1.04, 4.93], 2.05, p = 0.040
Model 3	1.41 [0.93, 2.14], 1.62, p = 0.105	1.39 [0.92, 2.09], 1.56, p = 0.118	1.52 [0.97, 2.39], 1.82, p = 0.069	2.22 [1.03, 4.77], 2.05, p = 0.041
N	1877-2020	1877-2020	1877-2020	1877-2020

Notes: Generalized linear models with Poisson regression used for all outcomes; Z-values and p values obtained using Wald χ^2 test. MMSE: Mini-Mental State Examination. Model 1: unadjusted. Model 2: adjusted for age, sex, education, height, weight, living status, number of cardiovascular conditions, osteoarthritis, chronic pain, urinary incontinence, heel bone stiffness, number of categories medications with increased fall risk, fall history (if relevant), fear of falling, unsteadiness while walking, smoking status, depressive symptoms at baseline, MMSE, total choice reaction time, grip strength, visual acuity, orthostatic hypotension, follow-up duration. Model 3: adjusted for Model 2 + usual gait speed. For models including those with a history of falls: Model 1 (df = 1), Model 2 (df = 31), Model 3 (df = 32). For models excluding those with a history of falls: Model 1 (df = 1), Model 2 (df = 29), Model 3 (df = 30).

fall risk and fear of falling, and to have poorer grip strength and slower gait speed compared to those not on antidepressants. The number of falls reported at follow-up and stratified by antidepressant use at baseline is provided in Table 2. 24.8%−40.7% of those on antidepressants reported recurrent, injurious or unexplained falls at follow-up compared to 9.8% −18% of those not on antidepressants.

Taking antidepressants at baseline was associated with recurrent falls, injurious falls, and unexplained falls occurring during follow-up in unadjusted (Model 1, Table 3) and adjusted (Model 2, Table 3) analyses, although the magnitude of the effects was reduced in the adjusted models. After taking sociodemographic, physical, cognitive, and health related factors into account, antidepressants were associated with 1.37−1.64 times increased risk of future falls. Further adjusting for usual gait speed reduced the incidence risk ratio (IRR) by a small amount, however it did not fully explain these associations and baseline antidepressant use remained independently associated with an increased risk of injurious falls and unexplained falls (Model 3, Table 3). In participants with no history of falls, antidepressant use at baseline was independently associated with recurrent falls, unexplained falls and syncope (Model 2, Table 3) although only the effects observed for syncope remained when further adjusting for gait speed (Model 3, Table 3). The inclusion of gait speed explained a reasonable amount of the reduction in IRR for recurrent falls but it had a relatively small effect on the IRR for unexplained falls. Full final multivariate models for those with and without a history of falls are available in Tables 4 and 5.

TABLE 4. Final Multivariate Model of Associations Between Antidepressants at Baseline and Fall Outcomes in Those with A History of Falls

	Recurrent Falls		Injurious Falls		Unexplained Falls		Syncope	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Antidepressants	1.31	0.99,1.74	1.58	1.21,2.06**	1.49	1.04,2.13*	1.36	0.61,3.05
Age	1.00	0.99,1.02	1.01	0.99,1.03	1.01	0.98,1.03	1.00	0.97,1.03
Height	0.99	0.98,1.01	1.01	0.99,1.02	1.02	0.99,1.04	1.00	0.96,1.04
Weight	1.00	0.99,1.01	1.00	0.99,1.01	1.00	0.99,1.01	1.00	0.98,1.02
Depressive symptoms	1.00	0.99,1.02	1.01	1.00,1.02	1.02	1.01,1.04**	0.98	0.94,1.02
Grip strength	0.99	0.98,1.01	0.99	0.97,1.01	0.97	0.95,0.99**	1.01	0.97,1.04
Visual acuity	1.00	0.99,1.02	1.00	0.99,1.01	1.00	0.98,1.01	0.98	0.96,1.00
MMSE	1.01	0.95,1.07	0.99	0.94,1.04	0.99	0.92,1.06	0.99	0.86,1.13
Total reaction time	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00
Medications with fall risk	0.97	0.82,1.14	0.95	0.80,1.13	1.00	0.80,1.26	1.04	0.67,1.61
Follow-up duration	1.15	0.99,1.33	0.95	0.83,1.10	1.01	0.82,1.25	0.96	0.68,1.35
Sex (female)	0.73	0.52,1.03	1.46	1.01,2.10*	0.78	0.48,1.25	1.07	0.52,2.19
Education (secondary)	1.04	0.84,1.30	1.13	0.90,1.42	1.35	1.00,1.81*	1.05	0.60,1.86
Education (tertiary)	1.01	0.78,1.31	1.02	0.79,1.32	1.16	0.81,1.68	0.70	0.37,1.30
Lives with others	1.01	0.81,1.26	0.84	0.67,1.05	0.77	0.57,1.04	0.81	0.47,1.37
1 cardiovascular condition	1.08	0.87,1.35	1.05	0.82,1.33	0.99	0.72,1.35	0.67	0.34,1.31
2 cardiovascular conditions	1.22	0.85,1.75	0.78	0.47,1.30	1.64	1.01,2.67*	0.69	0.24,1.98
≥3 cardiovascular conditions	1.86	1.18,2.95***	1.32	0.78,2.25	1.66	0.84,3.27	2.82	0.99,8.06
Osteoarthritis	1.26	1.04,1.54*	1.23	1.00,1.52	1.18	0.88,1.59	1.05	0.60,1.84
Incontinence	1.30	1.03,1.64*	0.98	0.76,1.26	0.99	0.72,1.38	1.02	0.49,2.10
Chronic pain	1.12	0.91,1.38	1.16	0.93,1.44	1.03	0.76,1.39	0.91	0.55,1.51
Osteopenia	1.07	0.87,1.31	1.30	1.04,1.63*	1.16	0.85,1.58	0.89	0.55,1.44
Osteoporosis	1.00	0.74,1.36	1.03	0.75,1.41	0.76	0.49,1.19	0.77	0.34,1.73
Previous smoker	0.80	0.65,0.97*	0.91	0.74,1.10	0.80	0.60,1.08	0.66	0.39,1.12
Current smoker	0.83	0.62,1.11	0.66	0.46,0.94*	0.70	0.43,1.12	0.85	0.43,1.67
Orthostatic hypotension	1.21	0.98,1.48	1.22	0.98,1.51	1.44	1.08,1.92*	1.42	0.84,2.42
Unsteadiness	1.27	1.00,1.62*	1.29	1.01,1.63*	1.42	1.02,1.99*	1.48	0.83,2.65
1 fall	1.56	1.23,1.97***	1.36	1.07,1.72*	1.16	0.81,1.65	1.09	0.53,2.26
≥2 falls	2.59	2.09,3.22***	1.95	1.51,2.53***	2.12	1.54,2.91***	2.31	1.18,4.53*
Somewhat afraid of falling	1.43	1.16,1.77**	1.05	0.83,1.31	1.42	1.02,1.96*	0.95	0.50,1.83
Very much afraid of falling	1.22	0.88,1.69	0.93	0.63,1.37	1.42	0.92,2.19	1.46	0.54,3.94
Gait speed	0.99	0.99,1.00**	1.00	0.99,1.00	0.99	0.98,1.00**	1.00	0.98,1.01

Notes: Multivariate generalised linear models with Poisson regression used for all outcomes (df = 32); p values obtained using Wald χ^2 test. MMSE: Mini-Mental State Examination.

*p <0.05,
**p <0.01,
***p <0.001.

Sensitivity Analysis

While information on dosage and duration of antidepressant use is not available in TILDA, we did try to tease this out by looking at repeated exposure to antidepressants i.e., using a dichotomous variable to denote participants who reported no antidepressant use or use at Wave 1 only (n = 2,472) versus antidepressant use at Wave 1 and Wave 2 or 3 (n = 121). It is important to note that this does not distinguish between continuous and intermittent antidepressant use. When we conducted the analysis using repeated exposure as our predictor variable, we found independent associations with recurrent falls (IRR = 1.36 [95% confidence interval {CI}: 1.01−1.84], z = 2.02, p = 0.043, df = 34), injurious falls (IRR = 1.45 [95% CI: 1.08−1.94], z = 2.47, p = 0.014, df = 34), and unexplained falls (IRR = 1.65 [95% CI: 1.12−2.42], z = 2.54, p = 0.011, df = 34) in the fully adjusted models. In those with no history of falls in the past year, repeated antidepressant use was associated with unexplained falls in the fully adjusted model (IRR = 1.83 [95% CI: 1.16−2.90], z = 2.59, p = 0.010, df = 32).

CONCLUSION

Antidepressant use at baseline was associated with an increased risk of injurious and unexplained falls occurring over 4 years follow-up in community-

TABLE 5. Final Multivariate Model of Associations between Antidepressants at Baseline and Fall Outcomes in Those without A History of Falls

	Recurrent Falls		Injurious Falls		Unexplained Falls		Syncope	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Antidepressants	1.41	0.93,2.14	1.39	0.92,2.09	1.52	0.97,2.39	2.22	1.03,4.77*
Age	1.00	0.97,1.02	1.01	0.99,1.03	1.00	0.97,1.03	1.00	0.96,1.04
Height	0.99	0.97,1.01	1.01	0.99,1.03	1.02	1.00,1.05	1.02	0.97,1.07
Weight	1.00	0.99,1.01	0.99	0.98,1.01	1.00	0.99,1.01	1.01	0.98,1.03
Depressive symptoms	1.00	0.98,1.02	1.01	0.99,1.02	1.03	1.01,1.05*	1.00	0.96,1.04
Grip strength	1.00	0.98,1.02	0.99	0.97,1.01	0.97	0.95,1.00*	0.99	0.96,1.03
Visual acuity	1.00	0.98,1.01	1.00	0.99,1.01	0.99	0.97,1.00	0.98	0.95,1.00
MMSE	0.99	0.92,1.07	0.97	0.91,1.04	0.95	0.87,1.03	0.99	0.86,1.15
Total reaction time	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00	1.00	1.00,1.00
Medications with fall risk	1.07	0.85,1.34	1.03	0.82,1.29	1.11	0.81,1.52	1.32	0.80,2.19
Follow-up duration	1.16	0.95,1.41	0.89	0.76,1.05	0.98	0.76,1.27	0.96	0.65,1.41
Sex (female)	0.78	0.49,1.22	1.48	0.95,2.30	0.99	0.54,1.81	1.33	0.56,3.15
Education (secondary)	1.06	0.78,1.43	1.23	0.92,1.65	1.46	0.99,2.14	1.03	0.53,1.99
Education (tertiary)	0.99	0.69,1.41	1.07	0.76,1.51	1.11	0.68,1.80	0.72	0.35,1.48
Lives with others	1.05	0.77,1.44	0.82	0.61,1.10	0.72	0.49,1.06	0.89	0.49,1.64
1 cardiovascular condition	1.10	0.80,1.51	1.07	0.79,1.45	1.15	0.74,1.79	0.79	0.36,1.73
2 cardiovascular conditions	1.33	0.84,2.09	1.05	0.64,1.74	2.28	1.33,3.92**	0.68	0.20,2.34
≥3 cardiovascular conditions	2.36	1.41,3.96**	1.15	0.53,2.47	2.33	1.06,5.14	3.04	0.83,11.10
Osteoarthritis	1.20	0.91,1.59	1.25	0.96,1.63	1.27	0.87,1.87	1.01	0.51,1.99
Incontinence	1.30	0.90,1.87	0.98	0.70,1.36	1.09	0.70,1.71	1.14	0.54,2.43
Chronic pain	1.35	1.03,1.79*	1.35	1.04,1.75*	1.08	0.72,1.63	0.87	0.46,1.65
Osteopenia	0.93	0.70,1.23	1.26	0.96,1.66	0.95	0.62,1.45	0.97	0.59,1.59
Osteoporosis	0.80	0.53,1.20	0.81	0.54,1.22	0.62	0.35,1.09	0.99	0.41,2.38
Previous smoker	0.71	0.54,0.93*	0.91	0.70,1.16	0.83	0.56,1.23	0.62	0.34,1.14
Current smoker	0.64	0.42,0.96*	0.44	0.26,0.76**	0.76	0.44,1.30	0.99	0.49,2.02
Orthostatic hypotension	1.26	0.95,1.68	1.29	0.98,1.69	1.37	0.93,2.02	2.05	1.18,3.57*
Unsteadiness	1.21	0.86,1.69	1.06	0.76,1.49	1.18	0.73,1.90	1.00	0.43,2.30
Somewhat afraid of falling	1.49	1.10,2.01	1.15**	0.86,1.53	1.42	0.94,2.13	1.13	0.52,2.46
Very much afraid of falling	1.50	0.92,2.44	1.08	0.61,1.90	1.23	0.63,2.38	1.56	0.42,5.84
Gait speed	0.99	0.98,1.00	1.00*	0.99,1.00	0.99	0.98,1.00*	1.00	0.98,1.01

Notes: Multivariate generalized linear models with Poisson regression used for all outcomes (df = 30); Z-values and p values obtained using Wald χ^2 test. MMSE: Mini-Mental State Examination.
*p <0.05,
**p <0.01, ***p <0.001.

dwelling adults aged 60 and older. In addition, antidepressant use was associated with an increased risk of syncope in those with no history of falls in the year prior to baseline. These associations were independent of multiple covariates including sociodemographics and objective indicators of health-related function such as visual acuity, orthostatic hypotension, choice reaction time, and usual gait speed. While these variables partially explained the observed associations (by up to 40%), antidepressants were still independently associated with 1.49−1.58 times greater risk of falls.

These results add to previous research findings that antidepressants are independently associated with future recurrent and injurious falls in community-dwelling adults[7,8,11] although not in those with no history of falls.[7] Systematic reviews have reported conflicting results for the associations between antidepressants and falls, however these have typically included studies conducted in multiple settings i.e., including community-dwelling adults, inpatients, outpatients, and nursing home residents[23–25] which makes it difficult to compare to these results. In addition, previous analysis of cross-sectional TILDA data reported that tricyclic antidepressants, although moreso clinically relevant depressive symptoms (i.e., CES-D ≥16), were associated with an increased risk of reporting syncopal events in the past year.[9] Given the previously observed association between antidepressants and reduced gait speed[14] and that gait impairments are associated with an increased risk of falls,[26,27] our hypothesis was that gait speed would explain, at least partly, the association between antidepressants and falls, but we found little evidence to

support this except in the case of recurrent falls for those with no history of previous falls.

Antidepressants may increase the risk of falls and syncopal events through a number of mechanisms. First, there are potential effects due to sedation, impaired reaction time and balance, daytime drowsiness, increased nocturia, orthostatic hypotension, cardiac conduction or rhythm disturbances, and movement disorders.[1] In addition, older adults on antidepressants typically have greater comorbidity and are taking more medications making them more susceptible to side-effects and interactions between drugs.[28]

Second, vascular pathology may play an important role. Orthostatic hypotension was included as a covariate in our models above and has previously been associated with an increased risk of frailty, particularly slower gait speed,[29] cognitive decline,[30] late-life depression,[31] and taking antidepressants.[32] Orthostatic hypotension and resulting reduction in cerebral blood flow may lead to an increased burden of white matter hyperintensities particularly in the frontal region, and this has been supported by a study finding that the degree of orthostatic systolic blood pressure drop was associated with increased white matter hyperintensities in a group with depression.[33] In contrast, Geerlings et al. (2012) reported that antidepressants, but not depressive symptoms are associated with greater global brain atrophy, hippocampal atrophy, and white matter hyperintensities. Regardless, white matter hyperintensities have been associated with gait impairments, cognitive impairment, and falls.[34]

Third, clinically relevant depressive symptoms have been associated with an increased risk of falls, particularly unexplained falls[35] and syncopal events,[9] and antidepressant use may be a proxy for more persistent chronic symptoms.

The well-established and potentially serious implications of falls such as injury including fracture, reduced functional independence, reduced quality of life, institutionalisation, and death[36] highlight the importance of a comprehensive falls assessment to prevent falls.[37] Clinicians prescribing antidepressants should be aware of the increased risk of falls and consider if alternative treatment would be effective and preferable, when taking other risk factors into account. It is also important to note that antidepressants are not only prescribed for depression, but also anxiety, panic disorder, neuropathic pain, and urinary incontinence and they may be used for prolonged periods without review.[1] Polypharmacy is common in older adults and therefore, the potential interactions between antidepressants and other medications, particularly those that can increase the risk of falls, makes regular review of medications essential.

Strengths of this study include the nationally representative population-based sample of community-dwelling older adults, detailed data on medication usage, the wide range of available covariates and 4-year follow-up. Sensitivity analysis showed that repeated exposure to antidepressants over the three waves was associated with increased risk of several outcomes, although specific information about the duration of taking antidepressants was not available. Other limitations include the lack of racial and ethnic diversity in the sample and the retrospective recording of falls occurring in the past year, although this was addressed by having a more stringent definition of falls that would be less likely to be affected by recall issues i.e., defining recurrent falls as at least two falls. The sample also reported a low rate of antidepressant use compared to recent pharmacoepidemiological surveys, although previous research has highlighted the low rate of diagnosis and treatment of late life depression.[38] This and the high number of covariates included in the models may partly explain the limited findings. Excess alcohol consumption has also been associated with depression and falls, however inclusion of problem drinking based on the CAGE scale had minimal effect on our models. As this was captured in the self-completion questionnaire, it resulted in loss of approximately 200 cases, therefore this was not included in our final models. As mentioned above, this study is limited in that we did not collect information about the dosage or duration of taking antidepressants and there are low numbers in the specific antidepressant groups (n = 81 on selective serotonin reuptake inhibitors (SSRIs) (ATC code: N06AB); n = 23 on serotonin and norepinephrine reuptake inhibitors (ATC code: N06AX16); n = 30 tricyclic antidepressants (ATC code: N06AA), preventing further analysis in this area. Several studies have reported associations between SSRIs and falls,[7,8] however a recent systematic review reported the lack of causal evidence and cautioned against avoidance of SSRIs in the treatment of depression on the basis of increased risk of falls.[39] This also highlights a final limitation of this paper − there is significant overlap

between the risk factors for depression and antidepressant use and the risk factors for falls, therefore it is very difficult to talk about the independent effect of antidepressant use on falls. However, an ongoing randomized controlled trial examining antidepressant treatment on a range of outcomes including falls should provide valuable information on this relationship in the future.[40]

In conclusion, antidepressants were associated with an increased risk of injurious and unexplained falls occurring over 4 years follow-up in community-dwelling adults aged 60 and older, although gait speed explains very little of this relationship. The underlying mechanisms of these observed relationships is not clear although it may be related to underlying depression, vascular pathology, or direct effects of the medication. While antidepressants may be a suitable treatment in some cases, clinicians should review all available options to identify the best treatment option for an individual based on their existing risk factors for outcomes such as falls.

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