The Association Between Central Nervous System (CNS)-Active Medication Use and Fall-Related Injury in Older Adults with Dementia

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Abstract

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Introduction: Few studies have examined the association between central nervous system (CNS)-active medications and fall-related injury in older adults with dementia, a high-risk population. Prior studies have been limited to institutional settings. We evaluated the association between CNS-active medication use and fall-related injury in community-dwelling older adults with dementia.

Methods: The population was community-dwelling older adults aged ≥65 years with a research dementia diagnosis participating in the Adult Changes in Thought Study. From automated pharmacy data, we created a time-varying composite measure of CNS-active medication use, including benzodiazepines/sedatives, anticholinergics, antidepressants, antipsychotics, opioids, and skeletal muscle relaxants. CNS use was classified as: current (≤30 days before fall-related injury), recent (31-90 days before), past (91-365 days before), and non-use. The outcome was fall-related injury based on inpatient and outpatient diagnosis (ICD-9) and injury (E) codes. We calculated standardized daily doses (SDDs) for each CNS-active medication and summed the SDDs across medications. We estimated hazard ratios (HR) with 95% confidence intervals (CI) from Cox models using time since dementia onset as the time axis and adjusting for health and functional characteristics.

Results: Among 793 subjects with dementia, there were 303 fall-related injuries over a mean follow-up of 3.7 years (2,907 total person-years). Relative to non-use, the fall risk (hazard) was significantly higher for current use (HR 1.59; 95% CI 1.19-2.12), but not for past use (HR 0.84; 95% CI 0.55-1.29) or recent use (HR 0.94; 95% CI 0.59-1.69). When estimating a time-varying HR, the contrast in fall hazards between current and no use of CNS-active medications appeared greatest soon after dementia onset. We did not observe significant differences by dose.

Conclusion: Current use of CNS-active medications, but not total dose, was associated with fall-related injuries in community-dwelling older adults with dementia, which appeared greatest soon after dementia diagnosis. Time-varying differences in risk between current users and non-users could be explained by a variety of factors such as more careful prescribing as dementia progresses. Additional examination is needed to further our understanding of these phenomena.

Introduction

One in three community-dwelling older adults aged 65 years or older falls each year.[1] Among older adults, falls are associated with increased morbidity and mortality, representing the leading cause of fatal and non-fatal injury.[1] In older adults with dementia, the risk of falling is higher, with estimates ranging from two- to eight-fold greater, and the resulting health outcomes are even more devastating.[2,3,4,5,6] It is estimated that 5 million individuals in the United States currently have dementia, and with the aging population, this number is expected to climb to 13 million by 2050.[7,8,9] Thus, identifying modifiable risk factors for falls in older adults with dementia is a public health priority.

Various classes of medications have been associated with increased risk of falls in older adults without dementia. For example, in community-dwelling older adults without dementia, central nervous system (CNS)-active medications, such as antidepressants and anxiolytics, have been associated with an increased risk of falls.[10,11,12,13] However, little is known about how certain medications may affect risk of falls in older adults with dementia, and results from studies conducted in older adults without dementia may not generalize to those with dementia. There is evidence to suggest that older adults with dementia may be more sensitive to the CNS adverse effects of CNS-active medications (e.g., sedation).[14,15,16] As such, many CNS-active medications (e.g. anticholinergics, benzodiazepines, hypnotics) are considered to be potentially inappropriate for use in older adults with dementia due to risk of CNS adverse effects.[17]

Few studies to date have examined how CNS-active medications may affect fall risk in older adults with dementia, despite the fact that nearly 80% of community-dwelling older adults with dementia have been prescribed a CNS-active medication.[18] Prior studies of CNS-active medications and falls in older adults with dementia have been limited to institutional settings (e.g., nursing home or hospital).[19,20,21,22,23] These prior studies have found an increased risk of

falls or fractures associated with various classes of CNS-active medications, including antipsychotics, antidepressants, anxiolytics, and hypnotics. While the existing evidence suggests an association between CNS-active medications and fall risk in older adults with dementia, the findings may not generalize to the majority of older adults with dementia, whom reside in the community rather than in institutional settings.[24,25] In addition, prior studies in this area have not evaluated fall risk associated with CNS-active medication use at specific time points with regard to dementia diagnosis, such as newly diagnosed versus late stage, and thus have included a heterogeneous population in terms of stage of dementia. Overall, more robust pharmacoepidemiologic evidence (for example, including more valid identification of subjects with dementia and more comprehensive adjustment for covariates) is needed to better understand fall risk associated with CNS-active medication use in this patient population, including magnitude of risk and critical periods of risk. This will ultimately allow for future targeted interventions to be developed to help optimize CNS-active medication use and decrease risk of falls in community-dwelling older adults with dementia.

The objective of this study is to examine the association between CNS-active medication use and risk of fall-related injury in community-dwelling older adults with newly diagnosed dementia. Furthermore, this study aims to elucidate whether there is a dose-response association between CNS-active medication use and risk of fall-related injury in this patient population.

Methods

Data Source, Study Design, and Sample

This study used data from the Adult Changes in Thought (ACT) Study, an ongoing prospective cohort study in which patients aged 65 years and older have been randomly sampled from Kaiser Permanente (KP) Washington (formerly Group Health Cooperative), an integrated health care organization in Washington State.[26] ACT study participants are evaluated every two years to assess cognitive function using the Cognitive Abilities Screening Instrument (CASI).[27] Those individuals with a CASI score ≤85 undergo further in-depth evaluation to determine a diagnosis of dementia using a gold standard research definition. Subjects were included in the present study if they had a diagnosis of dementia as of April 30, 2014, were enrolled in KP for at least one year prior to dementia diagnosis, and had no history of fall-related injury within one year prior to dementia diagnosis (n = 862). A study flow diagram is depicted in **Figure 1**.

Outcome Measurement

The outcome of fall-related injury was identified using ICD-9 and injury (E) codes for emergency department, inpatient, and outpatient claims, which was adapted from Tinetti et al (**Appendix Table 1**).[28] We selected fall-related injury as our outcome of interest given that it represents the most medically serious consequence of a fall, short of death.

Exposure Measurement

CNS-active medication use was ascertained from KP automated pharmacy data, which included outpatient prescription fills at KP pharmacies and prescription claims for fills at non-KP pharmacies. The CNS-active medications included were benzodiazepines, sedative hypnotics, anticholinergics, opioids, antidepressants, skeletal muscle relaxants, and antipsychotics. CNS-active medication use was defined dichotomously (yes/no) into the following mutually exclusive categories: a) current use: any overlap of an episode of use within 0-30 days before the fall, b)

recent use: any overlap of an episode of use within 31-90 days before the fall, c) past use: any overlap of an episode of use within 91-365 days before the fall, and d) non-use: no overlap of an episode of use within 0-365 days before the fall. To evaluate a potential dose-response relationship, total CNS-active medication burden was measured for current users by calculating standardized daily dose (SDD). SDD was calculated by dividing the total daily dose of each medication by the minimum effective geriatric dose for that medication (determined via a standard reference) and summing standardized doses of all CNS-active medications for each patient.[29,30] This approach for calculating SDD has been published in prior studies.[31,32] For a secondary analysis, risk of fall-related injury associated with new initiation of a CNS-active medication was examined. New initiation was defined as no evidence of a prescription fill for a CNS-active medication within the year prior to dementia onset. A complete list of CNS-active medications included in the analyses and the corresponding minimum effective doses used to calculate SDD are outlined in **Appendix Table 2**.

Covariates

Several demographic, health, and functional characteristics were measured to address potential confounding. Demographic covariates were age, ACT study cohort (original, expansion, replacement), sex, race (Caucasian or non-Caucasian), and education level (education beyond high school or not). Health characteristics gathered from the ACT interview most proximal to dementia onset were body mass index (BMI), self-rated health (fair or poor), poor vision (based on eyesight interview responses or inability to complete CASI test due to poor eyesight), osteoarthritis, coronary artery disease (myocardial infarction, angina, coronary artery bypass graft, or angioplasty), congestive heart failure, and prior stroke. Treatment for hypertension and treatment for diabetes were ascertained via prescription fills for related medications within three years prior to dementia onset. In addition, gait speed was measured as a marker of frailty during the ACT interview most proximal to dementia onset (<0.6 meters/second or inability to complete

the timed walk). For individuals missing this performance-based gait speed measure, a self-reported measure of activities of daily living related to walking was used for imputation of gait speed. To account for potential confounding by indication, the following conditions were adjusted for using ICD-9 codes and treated as time-varying (ever/never), with measurement starting three years prior to dementia onset: anxiety, Parkinson's disease, and urinary incontinence (**Appendix Table 3**). Depression was measured using a Center for Epidemiological Studies Depression (CESD) score of ≥16 or presence of an ICD-9 code, and was also treated as time-varying (ever/never). Behavioral disturbances of dementia and insomnia or sleep problems were also measured using ICD-9 codes and treated as time-varying, being updated over time with a 12-month look back period to capture their symptomatic nature.

Statistical Analyses

For the primary analysis, Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of fall-related injury associated with CNS-active medication use (current, recent, or past, compared with no use as the reference group). These models used time since dementia onset as the time axis and were adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, coronary artery disease, poor vision, congestive heart failure, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia. Furthermore, HRs and 95% CIs were estimated for risk of fall-related injury associated with level of SDD for current use (less than 1 SDD, 1 to <2 SDD, or ≥2 SDD) compared to no use as the reference group. A trend test was used to evaluate a potential dose-response relationship between SDD level compared to no use. As a secondary analysis, HRs and 95% CIs were estimated for risk of fall-related injury associated with new initiation of a

CNS-active medication. In this analysis, any new initiation of a CNS-active medication and prevalent use of a CNS-active medication (without new initiation) were compared with no use as the reference group. All analyses used a complete case analysis, excluding subjects with missing covariate data.

Examination of Schoenfeld residuals showed some evidence of non-proportional hazards for the comparison of current use to non-use of CNS-active medications. Thus, we conducted a post-hoc analysis in which an interaction between current CNS-active medication use and time after dementia onset, modeled using a natural cubic spline, was used to estimate a time-varying hazard ratio for the comparison of fall-related injury between current and non-users.[33]

Results

By April 30, 2014, 1,032 ACT subjects had a diagnosis of dementia. From this cohort, 63 subjects were excluded due to not having at least one year of enrollment in KP prior to dementia diagnosis. In addition, 107 subjects were excluded given evidence of a fall-related injury within one year prior to dementia diagnosis. This resulted in a sample of 862 subjects. The median age of the sample was 85 years, 61.5% of individuals were female, and 90.6% were Caucasian. Additional baseline characteristics and covariate information for the study population, further subdivided by category of CNS-active medication use, are detailed in **Table 1**. Of the 862 subjects, 335 (38.9%) were current users of any CNS-active medication, 57 (6.6%) were recent users, 106 (12.3%) were past users, and 364 (42.2%) were non-users.

Of the 862 subjects in the study population, 69 (8%) were excluded for the complete case analysis given missing covariate data, specifically BMI, self-rated health, or gait speed. Among the remaining 793 subjects, there were 303 fall-related injuries over a mean follow-up of 3.7 years (2,907 total person-years). Compared to no use of CNS-active medications and adjusting for covariates, current users had an increased risk of fall-related injury (adjusted HR 1.59, 95% CI 1.19 to 2.12). However, an increased risk of fall-related injury was not observed for recent users (adjusted HR 0.94, 95% CI 0.52 to 1.69) or past users (adjusted HR 0.84, 95% CI 0.55 to 1.29), compared to no use. Among current users, when comparing the various levels of SDD to no use, there was lack of a dose-response relationship. The trend test resulted in a p-value of 0.14. **Table 3** outlines the results of the secondary analysis. The adjusted HR for risk of fall-related injury associated with any new initiation of a CNS-active medication compared with no use was 1.86 (95% CI 0.85 to 4.09).

On post-hoc analysis, we examined how the HR for risk of fall-related injury associated with current CNS-active medication use (compared to no use as the reference group) may vary

based on time since dementia onset. The contrast in fall-related injury hazards between current and non-use of CNS-active medications appeared greatest soon after dementia onset, with a decline in HR over time following dementia onset. (**Figure 2**).

Discussion

In this sample of community-dwelling older adults with newly diagnosed dementia, current use of CNS-active medications was associated with an increased risk of fall-related injury compared to non-use (HR 1.59) over a mean follow-up of 3.7 years. Conversely, an increased risk was not observed for recent use or past use compared to non-use. The risk of fall-related injury observed with current CNS-active medication use did not differ by dose as measured by SDD.

Use of multiple CNS-active medications has been shown to increase risk of falls in older adults without dementia.[17,34,35] It was unexpected that we did not find a dose-response relationship in this sample of older adults with dementia. A prior observational cohort study by Sterke et al. conducted among nursing home residents with dementia also examined the impact of multiple CNS-active medications on fall risk.[20] However, this study evaluated unadjusted incident rates of falls for their assessment of specific concomitant medication combinations. Another important difference was that this study was conducted among nursing home residents, whereas ours focused on community-dwelling individuals. The outcome measure of this study also differed (fall noted in computerized report versus fall-related injury ascertained via ICD-9 and E codes). For these reasons, a direct comparison between studies is challenging.

Most prior studies evaluating the association between CNS-active medication use and falls or fractures in older adults with dementia have focused on single medication classes. The study by Sterke et al. evaluated fall risk associated with the individual classes of antipsychotics, antidepressants, anxiolytics, and hypnotics, and found an increased risk with each, including a dose-response relationship within each individual class.[20] A nested case-control study by Jalbert et al. also conducted among nursing home residents with dementia found an increased risk of hip fracture associated with use of typical and atypical antipsychotics.[22] In addition, a matched case-control study by Tamiya et al. identified an increased risk of fracture with use of sedatives

and hypnotics in hospitalized patients with dementia.[19] Given that our study evaluated CNS-active medications as a whole and did not look at single classes of medications, and our outcome measure also differed from those used in prior studies, our results cannot be directly compared to the results of these prior studies. Nonetheless, our study adds to the literature on medication-related fall risk in older adults with dementia by elucidating the risk of CNS-active medication use and fall-related injury in the community setting, where the majority of older adults with dementia reside. Moreover, our study was able to examine this association in older adults with a research quality gold-standard dementia diagnosis at a time point soon after diagnosis.

Initiation of a new CNS-active medication is often considered a high risk time during which a patient may be more susceptible to adverse effects of the medication, such as fall-related injury. The results of our secondary analysis showed a HR of 1.86 for risk of fall-related injury associated with new initiation of a CNS-active medication compared with no use, suggesting an increased risk, which was not statistically significant and had a wide 95% CI. This was likely influenced by the small sample size and low event rate in this secondary analysis. Ultimately, this association will need to be evaluated in a larger sample to further explore risk of fall-related injury associated with new initiation of CNS-active medication in older adults with dementia.

Additionally, given that older adults with dementia are a heterogeneous population with regard to stage of dementia, it is important to elucidate how risk of fall-related injury associated with CNS-active medication use may differ depending on time since dementia onset. Our post-hoc analysis evaluating a time-varying HR for risk of fall-related injury associated with current CNS-active medication use compared to no use following dementia onset showed the greatest HR soon after dementia onset, with a declining HR over time. It is important to consider the time-varying HR when interpreting the HR of 1.59 from the primary analysis, as this HR represents

an average over various time points. Time-varying differences in risk between current users and non-users seen in the present study could be explained by a variety of factors. One possibility is that prescribers are more cautious with regard to prescribing CNS-active medications as dementia progresses. Ultimately, additional exploration is needed to further our understanding of these phenomena.

The present study has many strengths. One strength is that individuals with dementia were identified using a research-quality diagnosis of dementia, rather than claims-based diagnosis codes, resulting in a study cohort for which dementia was well characterized and valid. This also allowed us to examine the associations of interest at a specific time point relative to dementia onset, rather than having a potentially much more heterogeneous population of subjects with dementia regarding time since diagnosis. Another strength of our study was that our exposure definition included several classes of CNS-active medications, some of which have not been included in prior studies evaluating risk of falls or fractures in older adults with dementia (e.g., opioids and anticholinergics). Additionally, we were able to measure total CNS-active medication burden and evaluate how this may influence risk of fall-related injury. Another strength was our ability to use ACT Study interview data in addition to administrative claims data, allowing us to adjust for several important covariates to minimize confounding (e.g., gait speed) that we would not have been able to adjust for using administrative claims data alone.

There are also limitations of our study. One limitation is that we relied on automated pharmacy data to ascertain exposure of CNS-active medication use, making misclassification of exposure a possibility due to uncaptured use of over-the-counter medications. However, this issue would be limited to the anticholinergic medications (e.g., antihistamines), as all other CNS-active medications included in this study are only available with a prescription. In addition, there is the possibility that an individual received a prescription for a CNS-active medication but never

actually used the medication, which could also result in misclassification of exposure. Another limitation of this study is that we may not have controlled for all possible confounders, and residual confounding may also have occurred. Finally, although our study was able to evaluate overall CNS-active medication burden, it did not assess effects of individual classes of CNS-active medications. Thus, it is possible that the results we observed are largely influenced by one or two specific classes of medications.

In conclusion, this study found that current use of CNS-active medications, but not total dose, was associated with risk fall-related injury in community-dwelling older adults with newly diagnosed dementia. When looking at time-varying HR, risk of fall-related injury associated with CNS-active medication use appeared greatest soon after dementia diagnosis. The results of this study suggest that soon after dementia diagnosis may represent a critical time point with regard to risk of fall-related injury associated with CNS-active medication use, though additional evaluation is needed to better understand how risk may change over time following dementia onset. This will be important in order to develop targeted interventions at critical time points to most optimally decrease risk of fall-related injury. In addition, future work is needed to evaluate risk of fall-related injury associated with specific classes of CNS-active medications in this population. Overall, the results of this study elucidate risk associated with use of CNS-active medications in community-dwelling older adults with dementia, and consequently highlight the need for cautious prescribing, judicious use, and close monitoring of these medications in this population.

Tables and Figures

Table 1. Baseline characteristics of Adult Changes in Thought (ACT) Study participants with dementia, by central nervous system (CNS)-active medication exposure.

	All Participants		CNS-Active Medication Exposure Classification							
			Non-Use		Past Use		Recent Use		Current Use	
	N = 862		N = 364		N = 106		N = 57		N = 335	
	N	%	N	%	N	%	N	%	N	%
Age, median (25th, 75th)	85 (81, 89)		84 (80, 88)		84 (80, 88)		86 (83, 89)		85 (81, 89)	
BMI, median (25th, 75th)	26 (23, 29)		26 (23, 29)		27 (23, 30)		26 (23, 30)		26 (24, 30)	
Sex										
Female	530	61.5	216	59.3	57	53.8	42	73.7	215	64.2
Male	332	38.5	148	40.7	49	46.2	15	26.3	120	35.8
Race										
Caucasian	781	90.6	329	90.4	96	90.6	54	94.7	302	90.1
Non-Caucasian	81	9.4	35	9.6	10	9.4	3	5.3	33	9.9
ACT cohort										
Original	621	72.0	256	70.3	81	76.4	39	68.4	245	73.1
Expansion	161	18.7	73	20.1	17	16.0	15	26.3	56	16.7
Replacement	80	9.3	35	9.6	8	7.5	3	5.3	34	10.1
Some education beyond high school	492	57.1	208	57.1	62	58.5	32	56.1	190	56.7
Fair or poor self-rated health	189	22.2	53	14.7	28	26.4	10	17.5	98	30.0
Frail according to gait speed	237	29.4	89	25.6	36	36.4	16	29.6	96	31.4
Treatment for hypertension	601	69.7	227	62.4	72	67.9	44	77.2	258	77.0
Treatment for diabetes	91	10.6	35	9.6	10	9.4	5	8.8	41	12.2
Osteoarthritis	577	66.9	229	62.9	64	60.4	40	70.2	244	72.8
Coronary artery disease	244	28.3	81	22.3	34	32.1	18	31.6	111	33.1
Poor vision	361	41.9	146	40.1	48	45.3	22	38.6	145	43.3
Congestive heart failure	88	10.2	24	6.6	14	13.2	4	7.0	46	13.7
Stroke	76	8.8	28	7.7	13	12.3	5	8.8	30	9.0
Anxiety	105	12.2	13	3.6	16	15.1	11	19.3	65	19.4
Depression (CESD score or ICD-9 code)	289	33.5	49	13.5	38	35.8	19	33.3	183	54.6
Urinary incontinence	149	17.3	35	9.6	25	23.6	13	22.8	76	22.7
Parkinson's disease	19	2.2	5	1.4	5	4.7	0	0.0	9	2.7
Insomnia or sleep problems	60	7.0	5	1.4	5	4.7	5	8.8	45	13.4
Behavioral disturbances of dementia	11	1.3	2	0.5	2	1.9	0	0.0	7	2.1

Abbreviations: ACT = Adult Changes in Thought, CNS = central nervous system, BMI = body mass index, CESD = Center for Epidemiological Studies Depression

Table 2. Association between CNS-active medication use and fall-related injury in Adult Changes in Thought Study participants with dementia, adjusting for covariates

CNS-Active Medication Use Group	Subjects[a] N = 793[b]	Fall-Related Injury N = 303	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
None	226	96	1.00 (Reference)	1.00 (Reference)
Past	74	29	0.88 (0.58, 1.33)	0.84 (0.55, 1.29)
Recent	33	13	0.98 (0.55, 1.76)	0.94 (0.52, 1.69)
Current[c]	460	165	1.68 (1.30, 2.16)	1.59 (1.19, 2.12)
<1 SDD	82	38	1.99 (1.36, 2.89)	1.77 (1.19, 2.62)
1 to <2 SDD	110	58	1.95 (1.40, 2.70)	1.79 (1.25, 2.56)
≥2 SDD	268	69	1.39 (1.02, 1.90)	1.35 (0.96, 1.92)

Abbreviations: HR = hazard ratio, CI = confidence interval, SDD = standardized daily dose

[a]At end of follow-up

[b]For complete case analysis

[c]The p-value for the trend test was 0.14 (not significant at 0.05 level)

[d]Adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, CAD, poor vision, CHF, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia.

Table 3. Association between new initiation of CNS-active medication and fall-related injury in Adult Changes in Thought Study participants with dementia, adjusting for covariates

CNS-Active Medication Use Group	Subjects[a] N = 343[b]	Fall-Related Injury N = 117	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]
None	214	86	1.00 (Reference)	1.00 (Reference)
Current (none newly initiated)	75	24	1.23 (0.77, 1.97)	1.30 (0.76, 2.21)
Any new initiation	54	7	1.76 (0.81, 3.81)	1.86 (0.85, 4.09)

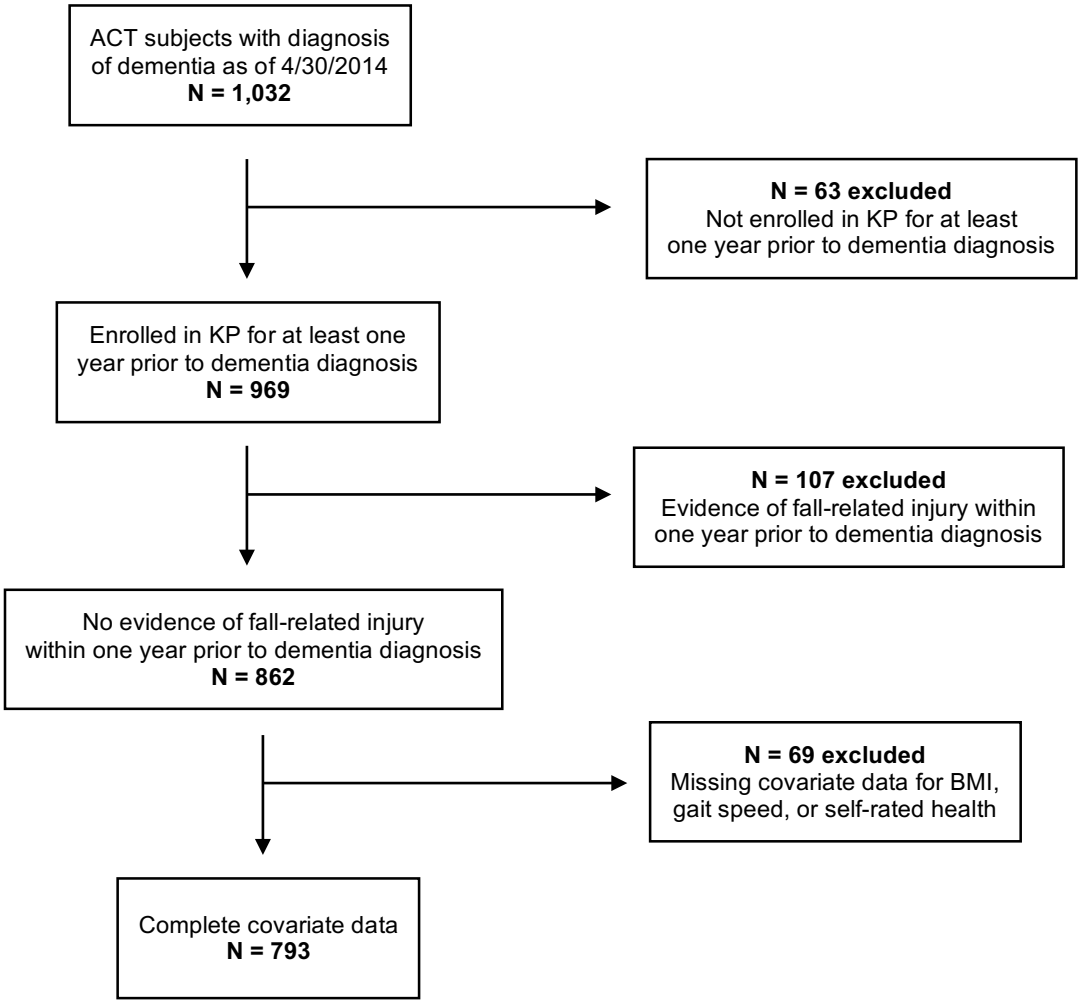
Abbreviations: HR = hazard ratio, CI = confidence interval

[a]At end of follow-up

[b]For complete case analysis

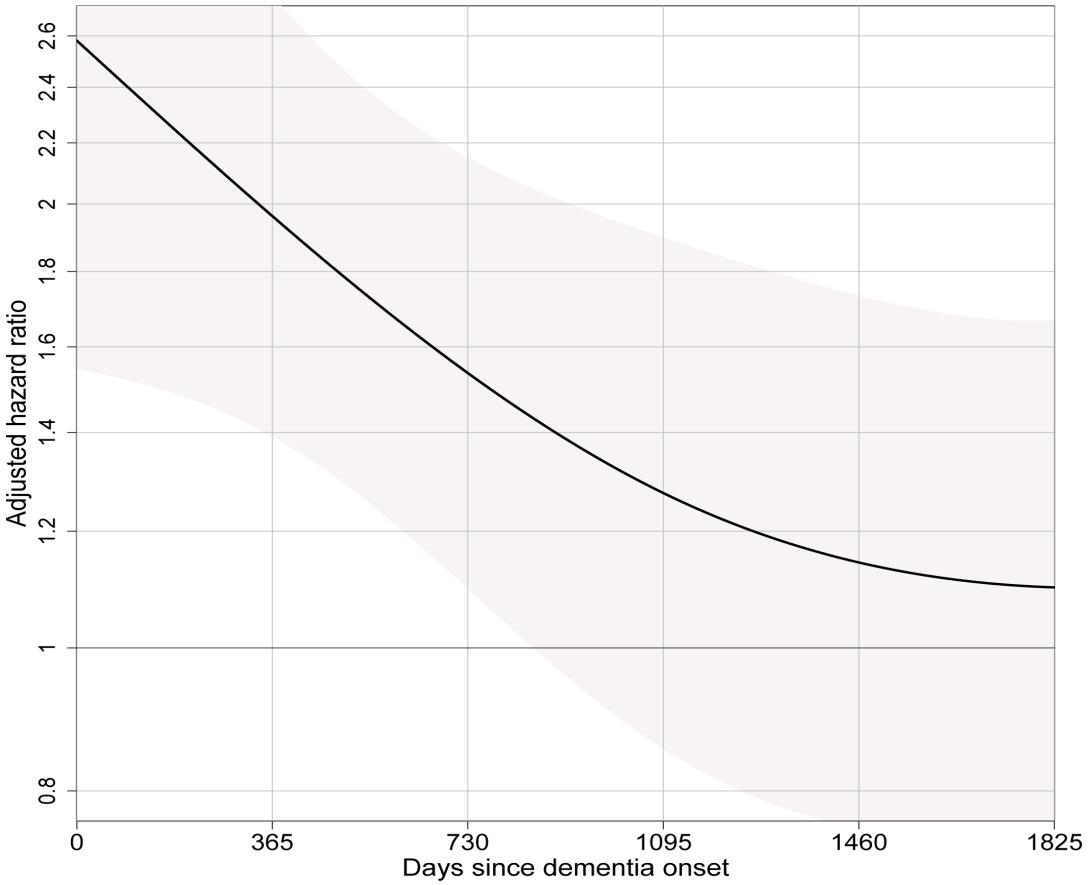
[c]Adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, CAD, poor vision, CHF, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia.

Figure 1. Eligibility criteria and sample size



Abbreviations: ACT = Adult Changes in Thought, KP = Kaiser Permanente

Figure 2. Fall-related injury hazards for current use of CNS-active medications relative to non-use in Adult Changes in Thought Study participants with dementia



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Appendix

Appendix Table 1. Diagnosis (ICD-9) codes and injury (E) codes used for fall-related injury

ICD-9 or E Code	Definition
Fracture	
800	Fracture of vault of skull
801	Fracture of base of skull
802	Fracture of face bones
803	Other and unqualified skull fractures
804	Multiple fractures involving skull or face with other bones
805	Fracture of vertebral column without mention of spinal cord injury
806	Fracture of vertebral column with spinal cord injury
807.0-807.2	Fracture of rib(s), sternum, larynx, and trachea
808.0-808.9	Fracture of pelvis
810	Fracture of clavicle
811	Fracture of scapula
812	Fracture of humerus
813	Fracture of radius and ulna
814	Fracture of carpal bone(s)
815	Fracture of metacarpal bone(s)
816	Fracture of one or more phalanges of hand
817	Multiple fractures of hand bones
818.0-818.1	Ill-defined fractures of upper limb
819.0-819.1	Multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
820	Fracture of neck of femur
821	Fracture of other and unspecified parts of femur
822	Fracture of patella
823	Fracture of tibia and fibula
824	Fracture of ankle
825	Fracture of one or more tarsal and metatarsal bones
826	Fracture of one or more phalanges of foot
827	Other multiple and ill-defined fractures of lower limb
828	Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum
829	Fracture of unspecified bones
Intracranial Injury	
850	Concussion
851	Cerebral laceration and contusion
852	Subarachnoid subdural and extradural hemorrhage following injury
853	Other and unspecified intracranial hemorrhage following injury
854	Intracranial injury of other and unspecified nature
Dislocation	
830	Dislocation of jaw
831	Dislocation of shoulder
832	Dislocation of elbow
833	Dislocation of wrist
834	Dislocation of finger

835	Dislocation of hip
836	Dislocation of knee
837	Dislocation of ankle
838	Dislocation of foot
839	Other multiple and ill-defined dislocations
Contusion	
920	Contusion of face, scalp, and neck except eye(s)
921	Contusion of eye and adnexa
922	Contusion of trunk
923	Contusion of upper limb
924	Contusion of lower limb and of other and unspecified sites
Accidental Fall	
E880	Accidental fall on or from stairs or steps
E881	Accidental fall on or from ladders or scaffolding
E882	Accidental fall from or out of building or other structure
E883	Accidental fall into hole or other opening in surface
E884	Other accidental falls from one level to another
E885	Accidental fall on same level from slipping tripping or stumbling
E886	Fall on same level from collision, pushing, or shoving, by or with other person
E887	Fracture, cause unspecified
E888	Other and unspecified fall
V15.88	History of falls

Appendix Table 2. CNS-active medications included in analysis and corresponding geriatric dose used to calculate standardized daily dose.

Drug Class	Individual Medications	Geriatric Daily Dose
Benzodiazepines		
	Alprazolam	0.25 mg
	Chlordiazepoxide	10 mg
	Clonazepam	0.5 mg
	Clorazepate	7.5 mg
	Diazepam	1 mg
	Eszopiclone	1 mg
	Lorazepam	0.5 mg
	Oxazepam	20 mg
	Temazepam	7.5 mg
	Triazolam	0.0625 mg
	Zaleplon	5 mg
	Zolpidem	5 mg
Anxiolytics and Hypnotics		
	Buspirone	15 mg
	Chloral hydrate	250 mg
Opioids		
	Codeine	200 mg (0.15)[a]
	Fentanyl transdermal	12.5 mg (2.4)
	Hydrocodone	30 mg (1.00)
	Hydromorphone	7.5 mg (4.00)
	Meperidine	300 mg (0.10)
	Methadone	10 mg (3.00)
	Morphine	30 mg
	Opium tinctures/suppositories	300 mg (0.10)
	Oxycodone	20 mg (1.5)
	Propoxyphene	130.4 mg (0.23)
	Tramadol	300 mg (0.10)
Antipsychotics		
Anticholinergic	Chlorpromazine	10 mg
	Clozapine	12.5 mg
	Olanzapine	5 mg
	Thioridazine	10 mg
Non-Anticholinergic	Aripiprazole oral	10 mg
	Haloperidol oral	0.5 mg
	Perphenazine (all combinations)	12 mg
	Quetiapine	50 mg
	Risperidone oral	1 mg
	Ziprasidone	40 mg
Antidepressants		
	Desipramine	25 mg
	Nortriptyline	30 mg
Anticholinergic: Tertiary Amine TCA	Amitriptyline	10 mg
	Doxepin	10 mg

	Imipramine	25 mg
Anticholinergic: Other (SSRI)	Paroxetine	10 mg
Non-Anticholinergic: SSRIs	Citalopram	20 mg
	Escitalopram	10 mg
	Fluoxetine	20 mg
	Sertraline	25 mg
Non-Anticholinergic: SNRIs	Duloxetine	20 mg
	Venlafaxine	50 mg
Non-Anticholinergic: Other	Bupropion	150 mg
	Maprotiline	25 mg
	Mirtazapine	15 mg
	Trazodone	25 mg
Skeletal muscle relaxants		
Anticholinergic	Cyclobenzaprine	5 mg
Non-Anticholinergic	Baclofen	10 mg
	Methocarbamol	600 mg
	Tizanidine hydrochloride	12 mg
Anticholinergics		
	Hydroxyzine	75 mg
	Prochlorperazine	15 mg
	Promethazine	50 mg
	Scopolamine oral	0.0195 mg
	Scopolamine patch	0.33 mg
Anti-Parkinson's	Benztropine	0.5 mg
	Trihexyphenidyl	6 mg
Genitourinary Antispasmodic	Darifenacin	7.5 mg
	Oxybutynin oral	5 mg
	Tolterodine	2 mg
	Trospium	20 mg
Gastrointestinal Anticholinergic/Antispasmodic	Atropine	0.0582 mg
	Belladonna suppository	1 suppository = 1 TSD
	Levorotatory alkaloids of belladonna	1 tablet = 1 TSD
	Dicyclomine	40 mg
	Homatropine	6 mg
	Hyoscyamine	0.75 mg
	Propantheline bromide	22.5 mg
Other		
Belladonna Extract	Alkaloids of belladonna leaf[b]	

Abbreviations: TCA = tricyclic antidepressants, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor, MAOI = monamine oxidase inhibitor

[a]For opioids, number in parentheses after dose refers to morphine equivalents

[b]Belladonna extract (16 mg) = 0.2 of alkaloids of belladonna leaf; each 0.2 mg of belladonna leaf = 0.0582 mg atropine, 0.0195 mg scopolamine, 0.3111 mg hyoscyamine

Appendix Table 3. ICD-9 codes used for covariates

ICD-9 Code	Definition
Depression	
296.2	Major depressive disorder, single episode
296.3	Major depressive disorder, recurrent episode
298.0	Depressive type psychosis
311	Depressive disorder, not elsewhere classified
300.4	Dysthymic disorder
301.12	Chronic depressive personality disorder
309.1	Prolonged depressive reaction
Anxiety	
300.0	Anxiety states
300.2	Phobic disorders
309.2	Adjustment disorder
Parkinson's Disease	
332.0	Primary Parkinsonism
Insomnia	
780.5	Sleep disturbances
327.0	Organic sleep disorders of initiating and maintaining sleep
Urinary Incontinence	
788.3	Urinary incontinence, unspecified
Behavioral Disturbances of Dementia	
293.0	Agitation