Cognitive enhancers associated with decreased risk of injury in patients with dementia: a nationwide cohort study in Taiwan

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ABSTRACT

This study aimed to investigate the associations among dementia, psychotropic medications and the risk of overall injuries. In this nationwide matched cohort study, a total of 144 008 enrolled patients ≥age of 50, with 36 002 study subjects who suffered from dementia and 108 006 controls matched for sex and age, from the Inpatient Dataset, for the period 2000–2010 in Taiwan were selected from the National Health Insurance Research Database, according to International Classification of Diseases, 9th Revision, Clinical Modification. When adjusting for the confounding factors, a Cox proportional hazards analysis was used to compare the risk of developing psychiatric disorders during the 10 years of follow-up. Of the study subjects, 6701 (18.61%) suffered injury when compared with 20 919 (19.37%) in the control group. The Cox regression analysis revealed that the study subjects were more likely to develop an injury (HR: 2.294, 95% CI=2.229 to 2.361, P<0.001) after adjusting for sex, age, monthly income, urbanization level, geographic region, and comorbidities. Psychotropic medications in the subjects with dementia were associated with the risk of injury (adjusted HR=0.217, 95% CI: 0.206 to 0.228, P<0.001). Cognitive enhancers, including acetylcholinesterase inhibitors and memantine, were associated with the risk of injury in the study subjects after being adjusted for all comorbidities and medications (adjusted HR=0.712(95% CI=0.512 to 0.925, P<0.01)). In conclusion, patients who suffered dementia had a higher risk of developing injury, and the cognitive enhancers were associated with the decreased risk of injury.

Significance of this study

What is already known about this subject?

- Previous studies had also found that dementia might well increase the risk of fractures and falling down injuries.
- Acetylcholinesterase inhibitors are known to improve gait performance, attention, and executive function in patients with dementia.
- Psychotropic medications showed varied impacts on patients with dementia in the risk of injury.

What are the new findings?

- Dementia is associated with increased risk of injury.
- To address a gap in knowledge, we investigated the association between cognitive enhancers and the reduced risk of injury in patients with dementia on the population database.
- The subjects with dementia were more likely to experience injury (HR: 2.294, 95% CI=2.229 to 2.361, P<0.001) when adjusting for sex, age, monthly income, urbanization level, geographic region, and comorbidities.

How might these results change the focus of research or clinical practice?

- If the association between cognitive enhancers and prevention of injury is causal, then the results would suggest a potential change in clinical practice.

INTRODUCTION

Dementia is a global public health problem,[1] and it was estimated that there were 46.8 million people living with dementia worldwide in 2015, and the estimated number of people with dementia could increase to 74.7 million by 2030, and 131.5 million by 2050, respectively.[2] In Taiwan, the prevalence was of 2–5% for the population aged ≥65 years in the community studies.[3–7] Meanwhile, the estimated global cost of dementia in 2010 was US$818 billion, which was 1.09% of the global gross domestic product (GDP), with the total direct costs accounting for 0.65% of the global GDP, and would thereby increase in proportion to the number of people with dementia.[8] The direct medical costs rose from US$96.4 billion in 2010 to US$159.2 billion in 2015. Dementia causes a significant increase in morbidity, mortality, and

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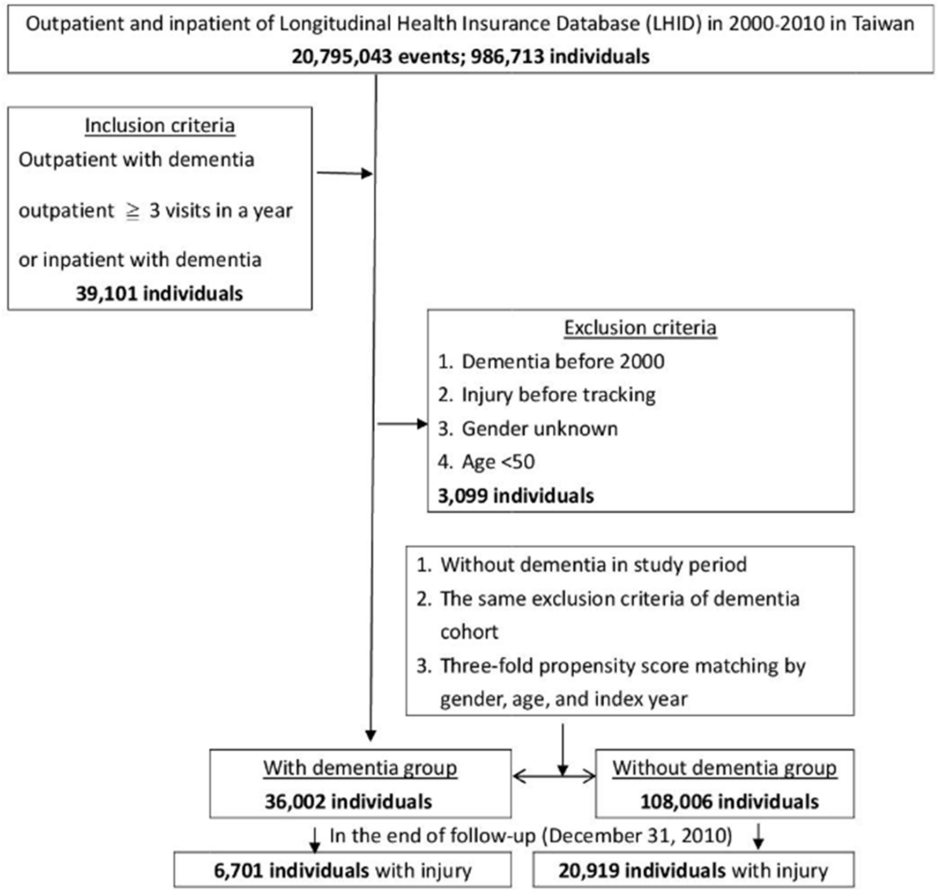

Figure 1 The flow chart of study sample selection from National Health Insurance Research Database in Taiwan.

consequently generating significant socioeconomic costs and burden for their caregivers and community.[7 9–11]

Previous studies had also found that dementia might well increase the risk of fractures and falling down injuries.[12 13] Conversely, injury, especially the traumatic type of brain injury increases the risk of dementia.[14 15] In previous studies, acetylcholine esterase inhibitors (AChEI) are known to improve gait performance, attention, and executive function in patients with dementia,[16–19] but negatively influence the bone mass formation and fracture healing capacity by inhibiting acetylcholine receptor in bone tissues.[20] These reports hint that AChEI may have different influences on the risk of injury of patients with dementia. Furthermore, studies on psychotropic medications, such as antidepressants, antipsychotics,[21] or benzodiazepines[22 23] also showed varied results. Therefore, a study for the association between newly onset dementia and the risk of overall injury has not, as yet, been clarified, and we therefore accomplished this study to elucidate this issue and the effects of the psychotropic medications, including cognitive enhancers, on the risk of injury for patients with dementia, in a nationwide, population-based study, using National Health Insurance Research Database (NHIRD) in Taiwan.

METHODS

Data sources

In this study, we have used data from the NHIRD to investigate the association between subjects with dementia and injury over a 10-year period from the total outpatient and hospitalization Longitudinal Health Insurance Database in Taiwan (2000–2010).

The National Health Insurance (NHI) program was launched in Taiwan in 1995, and as of June 2009, it included contracts with 97% of the medical providers with approximately 23 million beneficiaries or more than 99% of the entire population.[24] The NHIRD uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses.[25] All diagnoses of dementia were made by board-certified psychiatrists or neurologists, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), and its Text-Revised Edition (DSM-IV-TR),[26 27] as the injuries were confirmed by the injury care physicians, such as surgeons, traumatologists, or emergency medicine physicians, according to the clinical, laboratory, and image findings. Licensed medical records technicians would also review and verify the diagnostic coding before claiming the reimbursements in Taiwan's hospitals.[28] The NHI Administration randomly reviews the records for the ambulatory care visits and the inpatient claims to verify the accuracy of the diagnoses periodically.[29] Several studies have demonstrated the accuracy and validity of several diagnoses in the NHIRD, including diabetes mellitus (DM),[30 31] cancer,[32–34] myocardial infarction,[30 35 36] and central nervous system diseases, such as Tourette syndrome,[37] and stroke,[30 38–41] outcomes,[34] mortality,[30 42] or comorbidity.[34 42] In a wide

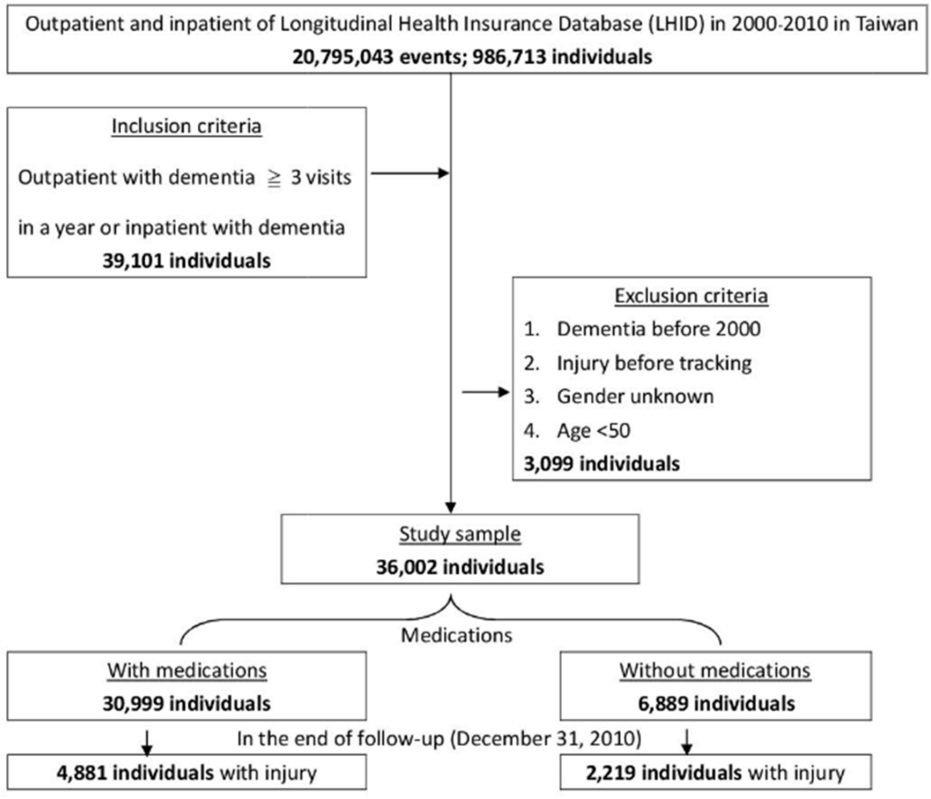

Figure 2 The flow chart of study sample selection from National Health Insurance Research Database in Taiwan.

spectrum of conditions, some studies also demonstrated concordance between Taiwan's National Health Survey and NHIRD on a variety of diagnoses,[43] medication use,[43] and health system utilizations.[43 44] Therefore, it is suitable to use the NHIRD for studying the association between dementia and the risk of injury, as well as the role of psychotropic medications, including cognitive enhancers, associated with the risk of injury in patients with dementia.

Study design and sampled subjects

This study was of a retrospective matched cohort design. Patients with dementia were selected from January 1, 2000 to December 31, 2000, according to the ICD-9-CM codes: ICD-9-CM codes: 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0. Three visits to the NHI-contracted medical providers in a year confirmed the dementia diagnosis collected. A total of 144 008 enrolled patients of age ≥50, including 36 002 subjects with dementia and 108 006 controls without dementia matched for age, sex, and index year, were selected in this study (figure 1). In the subjects with dementia, 30 999 used the psychotropic medications (defined below), and 6889 had not used any of the psychotropic medications in the follow-up period (figure 2).

Covariates

The covariates included sex, age group (50–64 years, ≥65 years), geographical area of residence (north, central, south, and east of Taiwan), urbanization level of residence (levels 1–4), levels of hospitals as medical centers, regional hospitals, and local hospitals, and monthly income (in New Taiwan Dollars (NT$); <18 000, 18 000–34 999, ≥35 000). The urbanization level of residence was defined according to the population and various indicators of the level of development. Level 1 was defined as a population of >1 250 000 and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500 000 and 1 249 999 and as playing an important role in the political system, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149 999 and 499 999 and <149 999 respectively.[45]

Comorbidity

Baseline comorbidities included DM (ICD-9-CM code: 250), hypertension (ICD-9-CM codes: 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, 405.9), hyperlipidemia (ICD-9-CM code: 272.x), coronary artery disease (CAD) (ICD-9-CM codes: 410–414), obesity (ICD-9-CM code: 278), chronic kidney disease (CKD, ICD-9-CM codes: 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 753, 403, 404, 2504, 2741, 4401, 4421, 4473, 5724, 6421, 6462), depression (ICD-9-CM codes: 296.2, 296.3, 296.82, 300.4, and 311), and stroke (ICD-9-CM codes: 430–438). Data on the use of psychotropic medications, including cognitive enhancers (acetylcholinesterase inhibitors (AChEI) and memantine), antipsychotics, antidepressants and Z-drugs, and benzodiazepines, were collected. The data of defined daily dose (DDD) were obtained from the WHO Collaborating

Table 1 Distribution of sex, age, comorbidity, urbanization, geography, and income of individuals with dementia and without dementia

Dementia	With		Without		
	n	%	n	%	
Variables	36 002	25.00	108 006	75.00	P
Sex					0.999
Male	19 600	54.44	58 800	54.44	
Female	16 402	45.56	49 206	45.56	
Age groups (years)					0.999
50–64	799	2.22	2397	2.22	
≥65	35 203	97.78	105 609	97.78	
Comorbidity					
DM	8005	22.23	21 102	19.54	<0.001
Hypertension	11 352	31.53	29 865	27.65	<0.001
Hyperlipidemia	925	2.57	3227	2.99	<0.001
CAD	3461	9.61	16 445	15.23	<0.001
HF	1458	4.05	5917	5.48	<0.001
Obesity	2	0.01	27	0.02	0.074
Chronic kidney disease	1677	4.66	8198	7.59	<0.001
Depression	1027	2.85	529	0.49	<0.001
Stroke	9902	27.50	14 362	13.30	<0.001
Urbanization level					<0.001
1 (the highest)	9715	26.98	33 848	31.34	
2	15 661	43.50	49 235	45.59	
3	2415	6.71	7547	6.99	
4 (the lowest)	8211	22.81	17 376	16.09	
Geography					<0.001
Northern Taiwan	12 932	35.92	43 056	39.86	
Middle Taiwan	10 868	30.19	30 396	28.14	
Southern Taiwan	8993	24.98	27 347	25.32	
Eastern Taiwan	3089	8.58	6670	6.18	
Outlets islands	120	0.33	537	0.50	
Income (NT$)					0.001
<18 000	35 772	99.36	107 105	99.17	
18 000–34 999	228	0.63	888	0.82	
≥35 000	2	0.01	13	0.01	

P value (χ^2/Fisher's exact test); DM, diabetes mellitus: ICD-9-CM 250; hypertension: ICD-9-CM 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, 405.9; hyperlipidemia: ICD-9-CM 272; CAD, coronary artery disease: ICD-9-CM 410–414; HF, heart failure: ICD-9-CM 428; obesity: ICD-9-CM 278; CKD, chronic kidney disease: ICD-9-CM 274.1, 403–404, 440.1, 442.1, 447.3, 572.4, 580–589, 642.1, 646.2, 753; depression: ICD-9-CM 296.2–296.3, 296.82, 300.4, 311; stroke: ICD-9-CM 430–438.

Centre for Drug Statistics Methodology (https://www.whocc.no/), and the duration of the use of drugs was calculated by dividing the cumulative doses by the DDD of drugs.

Outcome measures

All of the study participants were followed from the index date until the onset of injury (ICD-9-CM codes: 800.xx–999.xx), withdrawal from the NHI program, or the end of 2010. The severity of injury was classified as mild (treatment in the outpatient or emergency departments), moderate (hospitalization without Injury Severity Score (ISS)≥16), or severe (hospitalization with ISS ≥ 16). The injury diagnosis, causes, and intentionality were also recorded.

Statistical analysis

All analyses were performed using the SPSS software V.22 (SPSS Inc., Chicago, Illinois, USA). χ^2 and t-tests were used to evaluate the distributions of the categorical and continuous variables, respectively. The Fisher's exact test for the categorical variables was used to statistically examine the differences between the two groups. The missing data were handled by generalized estimating equation model; the first-order autoregression, or AR,[1] was used in working correlation matrix. The multivariate Cox proportional hazards regression analysis was used to determine the risk of injury, and the results were presented as a HR with a 95% CI. The difference in the risk of dementia, between the study and control groups, was estimated using the Kaplan-Meier method with the log-rank test. A two-tailed P value <0.05 was considered to indicate the statistical significance.

RESULTS

Sample characteristics

Table 1 shows the sex, age, comorbidities, urbanization, area of residence, and the income of the subjects with or without dementia. The subjects with dementia were more likely to have higher all comorbidity, residence in the lowest urbanization (Level 4), and in southern Taiwan,

Table 2 Factors of injury and subgroup of injury by using Cox regression

	With dementia			Without dementia			With versus Without		
Injury severity	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	P
Total	6701	49964.72	13411.46	20919	374918.24	5579.62	2.294	2.229 to 2.361	<0.001
Outpatient	4986	49964.72	9979.04	17041	374918.24	4545.26	2.302	2.227 to 2.380	<0.001
Inpatient	983	49964.72	1967.39	1667	374918.24	444.63	2.373	2.179 to 2.583	<0.001
ISS ≥16	782	49964.72	1565.10	2211	374918.24	589.73	2.091	19.15 to 2.283	<0.001
Sex									
Male	3634	26700.46	13610.25	10724	205214.96	5225.74	2.399	2.306 to 2.496	<0.001
Female	3067	23264.26	13183.31	10195	169703.28	6007.54	2.171	2.082 to 2.264	<0.001
Age groups (years)									
50–64	132	740.08	17835.91	315	4655.96	6765.52	2.411	1.937 to 3.000	<0.001
≥65	6569	49224.64	13344.94	20604	370262.28	5564.70	2.292	2.226 to 2.359	<0.001

Adjusted HR, adjusted for sex, age, comorbidity, urbanization, geography, and income; ISS, Injury Severity Score; PYs, person years.

and have a slightly greater proportion with lower monthly income (<18 000) than the control without dementia. In the subjects with dementia, there were 6923 (19.23%) of Alzheimer-type dementia (AD), 7424 (20.62%) of vascular dementia (VaD), and 21 655 (60.15%) of non-VaD (data not shown). In addition, for the group with dementia, there were 1872 in 36 002 (5.20%) missing data (losses to follow-up), and in the group without dementia, there were 5687 in 108 006 (5.25%) missing data. The total missing data were 7559 in 144 008 (5.25%). The difference of missing data in the two groups is not statistically significant.

Kaplan-Meier model for the cumulative risk of injury

In this study, the overall injury risk in the subjects with dementia was higher than the non-dementia control group, as well as in the risk of mild (those needing only outpatient treatment), the risk of moderate (those needing hospitalization), or severe injury (ISS ≥16) (table 2). The injury rates of subjects with dementia and non-dementia control are 18.61% in 36 002 and 19.37% in 108 006, respectively, and in two-tailed test, while setting the significance as P<0.05, the estimated statistical power for this study is 0.8875. Among the causes of injuries in the subjects with dementia, traffic accidents (3.6-fold, P<0.001), falling down injuries (4.0-fold, P<0.001), cutting/crushing/penetration (2.8-fold, P<0.001), and other unintentional injuries (2.8-fold, P=0.004), were higher than the non-dementia groups. In the 10-year follow-up, the reduction of risk was statistically significant in the patients with psychotropic medications (the log-rank test, P<0.001, figure 3). In addition, the durations of follow-ups were shown in online supplementary table 1.

HR analysis of injury in patients with dementia

The usage of psychotropic medications in subjects with dementia was associated with the risk of injury (0.217-fold, P<0.001, table 3). The use of psychotropic medications in subjects with dementia was associated with the following types of injuries: bone fractures (0.868-fold, P=0.001), vascular injuries (0.283-fold, P=0.007), crushing (0.276-fold, P=0.002), and other injuries (0.103-fold, P<0.001). The use of psychotropic medications in subjects with dementia attenuates the following causes of injuries: falling (0.870-fold, P=0.002), cutting/crushing/penetration (0.731-fold, P<0.001), and other unintentional injuries (0.696-fold, P<0.001) (online supplementary table 2). The use of psychotropic medications in subjects with dementia was associated with 0.810-fold (P<0.001) unintentional injury, therefore, in the intentionality of injury, the patients with dementia medications treatment have lower rates of unintentional injury than the non-medications group .In addition, the group of medication use duration of ≥365 days was associated with lower HR than the group of medication use duration of 1–364 days.

HR analysis of injuries in patients with psychotropic medications, including cognitive enhancers

The psychotropic medications for the treatment of dementia were grouped into four classes by the number of subjects who had used these medications: antipsychotics, cognitive enhancers, antidepressants, and benzodiazepines/Z-drugs. The cognitive enhancers, AChEI and memantine, were associated with the HRs of developing injuries while adjusted with the covariates, comorbidity, and antipsychotic usage.

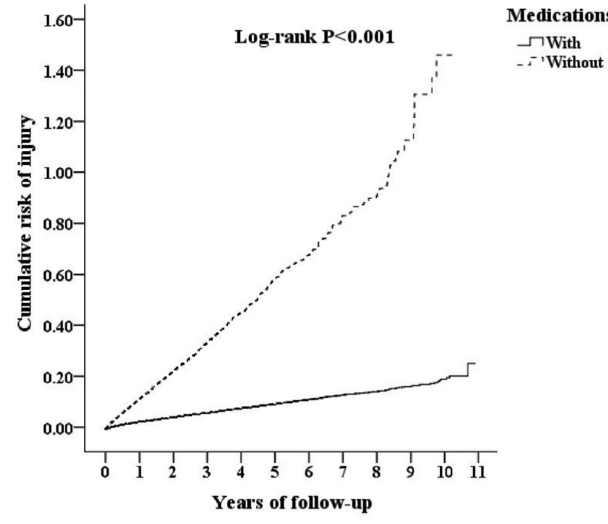

Figure 3 Kaplan-Meier plot for cumulative risk of injury among patients with dementia with aged 50 and over stratified by medications with log-rank test.

Table 3 Factors of injury among patients with dementia by using Cox regression

Variables	Crude HR	95% CI	P	Adjusted HR	95% CI	P	Adjusted HR	95% CI	P
Medications									
(Reference: without)	0.206	0.195 to 0.217	<0.001	0.217	0.206 to 0.228	<0.001			
Medications (days)									
(Reference: 0)									
1–364	0.249	0.221 to 0.269	<0.001				0.252	0.232 to 0.277	<0.001
≥365	0.198	0.145 to 0.219	<0.001				0.209	0.186 to 0.224	<0.001
Sex									
Male									
(Reference: female)	1.015	0.968 to 1.065	0.536	0.994	0.974 to 1.044	0.815	0.994	0.973 to 1.046	0.818
Age groups (years)									
≥65									
(Reference: 50–64)	0.761	0.641 to 0.904	0.002	0.751	0.632 to 0.893	0.001	0.750	0.634 to 0.895	0.002
Comorbidity									
(Reference: without)									
DM	0.828	0.779 to 0.879	<0.001	0.855	0.804 to 0.910	<0.001	0.855	0.806 to 0.911	<0.001
Hypertension	1.091	1.033 to 1.152	0.002	1.111	1.051 to 1.175	<0.001	1.112	1.050 to 1.176	<0.001
Hyperlipidemia	0.543	0.384 to 0.768	0.001	0.568	0.401 to 0.805	0.001	0.568	0.401 to 0.806	<0.001
CAD	0.639	0.581 to 0.703	<0.001	0.675	0.614 to 0.742	<0.001	0.677	0.618 to 0.747	<0.001
HF	0.404	0.353 to 0.462	<0.001	0.473	0.414 to 0.541	<0.001	0.472	0.415 to 0.543	<0.001
Obesity	6.864	0.966 to 48.534	0.054	2.021	0.284 to 14.372	0.482	2.019	0.265 to 13.397	0.479
Chronic kidney disease	0.640	0.578 to 0.710	<0.001	0.707	0.637 to 0.783	<0.001	0.708	0.640 to 0.787	<0.001
Depression	1.808	1.519 to 2.152	<0.001	1.676	1.407 to 1.996	<0.001	1.678	1.409 to 2.000	<0.001
Stroke	0.757	0.709 to 0.809	<0.001	0.752	0.704 to 0.804	<0.001	0.751	0.703 to 0.804	<0.001
Urbanization level									
(Reference: 4)									
1 (the highest)	0.775	0.723 to 0.831	<0.001	0.809	0.754 to 0.867	<0.001	0.808	0.754 to 0.872	<0.001
2	0.946	0.891 to 1.004	0.067	0.959	0.903 to 1.018	0.168	0.961	0.904 to 1.019	0.197
3	0.889	0.801 to 0.986	0.026	0.919	0.828 to 1.020	0.111	0.914	0.821 to 1.015	0.104
Geography									
(Reference: Northern Taiwan)				Had collinearity with urbanization level			Had collinearity with urbanization level		
Middle Taiwan	1.260	1.136 to 1.281	<0.001	Had collinearity with urbanization level			Had collinearity with urbanization level		
Southern Taiwan	1.140	1.070 to 1.215	<0.001	Had collinearity with urbanization level			Had collinearity with urbanization level		
Eastern Taiwan	1.343	1.234 to 1.461	<0.001	Had collinearity with urbanization level			Had collinearity with urbanization level		
Outlets islands	0.957	0.640 to 1.431	0.831	Had collinearity with urbanization level			Had collinearity with urbanization level		
Income (NT$)									
(Reference:<18 000)									
18 000–34 999	1.110	0.828 to 1.462	0.509	1.096	0.825 to 1.456	0.527	1.098	0.829 to 1.457	0.533
≥35 000	0	–	0.832	0	–	0.955	0	–	0.957

Adjusted HR: adjusted for sex, age, comorbidity, urbanization, geography, and income; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure.

Antidepressants were associated with the risk of injuries in the crude HR, but were of no significance when adjusted with other factors, such as comorbidity and antipsychotic usage. Antipsychotics and benzodiazepines/Z-drugs are not associated with reduced risk of injuries (table 4).

DISCUSSION

Association between dementia and the risk of injury

In our study of enrollees ≥age of 50, the risk of moderate (which needs hospitalization) or severe injury (ISS ≥16) in the subjects with dementia was higher than the non-dementia controls. People with dementia are disproportionately represented in injury-related hospitalizations, experience longer hospital lengths of stay, and have poorer outcomes.[46] Therefore, it has clinical significance to determine if the psychotropic medication could decrease injury risks (adjusted HR, 0.217). In our study, types of injury, injury diagnosis, and intentionality of injury along with psychotropic medication usage were discussed. To our knowledge, this might be the first study using the NHIRD to discuss the association of injury risks in subjects with dementia with psychotropic medication use.

Comparison of this study with previous literatures

One previous study reported an Australian cohort study showing that older adults with dementia were at a greater risk of hospital admission for an injury, but had lower risks of major injuries (ISS >15).[47] Their study has some differences from ours: we included all the patients with dementia in the outpatient or hospitalization setting from

Table 4 HRs of patients with dementia by medication use compared with patients without medication use

				Without antipsychotics	With antipsychotics
Medication use	**Injury n (%)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Antipsychotics					
Yes (n=28 462)	5389 (18.9%)	0.994 (0.852 to 1.091)	1.025 (0.942 to 1.125)		
No (n=115 546)	22 231 (19.2%)	Reference	Reference		
Antidementia drugs					
Yes (n=27 612)	4897 (17.7%)	0.709 (0.445 to 0.825)**	0.767 (0.608 to 1.028)	0.846 (0.756 to 1.154)	0.712 (0.512 to 0.925)*
No (n=116 396)	22 723 (19.5%)	Reference	Reference	Reference	Reference
Antidepressants					
Yes (n=27 513)	4207 (15.3%)	0.764 (0.584 to 0.972)*	0.835 (0.589 to 1.010)	0.911 (0.597 to 1.195)	0.803 (0.586 to 1.064)
No (n=116 495)	23 413 (20.1%)	Reference	Reference	Reference	Reference
Benzodiazepines and Z-drugs					
Yes (n=25 311)	5896 (23.3%)	1.271 (0.858 to 1.465)	1.162 (0.826 to 1.496)	1.194 (0.892 to 1.527)	1.124 (0.813 to 1.365)
No (n=118 697)	21 724 (18.3%)	Reference	Reference	Reference	Reference

Adjusted HR, adjusted for sex, age, comorbidity, urbanization, geography, income, and each drug; *P<0.01, **P<0.001.
Medication duration (days) per patient: donepezil: 264.7; rivastigmine: 289.5; galatamine: 300.4; memantine: 275.0.

the data set, rather than subjects with index hospitalization for dementia, and all the types of injuries, from minor injury which required only ambulatory clinics or emergency department treatment to severe injury that needed hospitalization were included in our study, instead of patients hospitalized for injuries only. However, both studies point out that the impact of injuries on the patients with dementia is important.

Possible mechanisms for the increased risk of injuries in patients with dementia

The comorbid diseases of patients with dementia, such as DM, hypertension, hyperlipidemia, CAD, HF, obesity, CKD, depression, and stroke, might be associated with weaker limb strength, impaired vision, unstable gait and balance, poor judgment, and poor impulse control and thus these could be the factors contributing to the results. Subjects with dementia may well be more vulnerable to being injured, but have lower activities of getting injured than the non-dementia ones, due to their poor physical condition and social withdrawal.

Psychotropic medications and the risk of injury in patients with dementia

In Taiwan, the most common psychotropic medications used in the patients with dementia were antipsychotics, sedative-hypnotics, and antidepressants,[48] and the cognitive enhancer usage was as low as 2.4% in all patients with degenerative dementia.[49] It this study, the psychotropic medication use for reducing the injury risks in the subjects with dementia had been discussed. The fact that the group of medication use duration of ≥365 days was associated with lower HR than the group of duration of 1–364 days might also support this finding. Cognitive enhancers lower the risk of injuries in the subjects with dementia versus the drug-naïve ones, while antidepressant loses its significance when adjusted with other factors. Patients with dementia with psychotropic medication usage were associated with a lower risk of injury from falling (0.870-fold, P=0.002), cutting/crushing/penetration (0.731-fold, P<0.001), and other unintentional injuries (0.696-fold, P<0.001), with the diagnoses of bone fractures (0.868-fold, P=0.001), vascular injuries (0.283-fold, P=0.007), crushing (0.285-fold, P=0.005), and other injuries (0.103-fold, (P<0.001).

The AChEIs might be associated with the increased cholinergic effects in bones, and thus being a positive factor in association with the risk of fractures in patients with AD. Several studies also showed that memantine had favorable effects on gait disturbances in AD and AD-related diseases.[17–19] However, a previous meta-analysis showed that memantine may have had a favorable effect on fracture, but no effects on falls, syncope, or accidental injury.[50] Therefore, we need more studies to clarify the actual mechanisms of AChEI and memantine on the fall-related injury, as well as other injuries.

In this study, antidepressants, antipsychotics, and benzodiazepines were noted to be associated with reduced risk of injury, after adjusted by age, sex, comorbidity, covariates, and other psychotropic medications. Previous studies reported that antidepressants, antipsychotics,[21] and benzodiazepines are associated with fall risk.[22 23] However, some reports have different results in other injuries such as fractures in the older age populations, even with studies using the cross-over design which focused on the recent or immediate effects of hypnotics.[51 52] More studies are needed to clarify the impact of these medications on the risk of injury in patients with dementia.

Limitations

There are some limitations worth noting in this study. First, there was no detailed information on patient characteristics such as information of lifestyle, nutritional status, or behavioral patterns from the NHIRD. Second, there was a lack of staging, severity, and functional status for the subjects with dementia. Third, given the same severity of injury, a patient with dementia would be more likely to be hospitalized than a patient without dementia, due to concerns about being able to manage the situations. Finally, in this claims data set, we could only record the prescribed dosages of the cognitive enhancers, but not the actual dosages the patients had taken in this study. Hence, further research is therefore required

to prove this observational trend. This claims data set could only provide cumulative doses of the medications, and the duration of use was calculated by dividing cumulative doses by DDD of these drugs.

CONCLUSIONS

Patients who suffered dementia had a higher risk of developing injury, and the psychotropic medications were associated with the decreased risk of injury (online supplementary figure).

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