ORIGINAL RESEARCH

The Association between Acupuncture Therapy and the Risk of Disability Development in Dementia Patients: A Nationwide Cohort Study

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Purpose: Disability is the comorbidity of dementia for which there is no available preventive measure. The aim of this study was to investigate the association between acupuncture treatment and the risk of disability development in dementia patients.

Patients and Methods: A cohort study was performed using a nationwide health database in Taiwan. The included dementia patients were divided into acupuncture and non-acupuncture cohorts based on whether they received acupuncture treatment during the follow-up period. The variables in the two cohorts were controlled by 1:1 propensity-score matching. The difference in disability development in dementia patients between the acupuncture and non-acupuncture cohorts was also analyzed. Subgroup analyses were performed using socioeconomic variables, comorbidities and anti-dementia agents (donepezil, rivastigmine, galantamine and memantine) used for dementia treatment.

Results: A total of 9,760 dementia patients met our inclusion criteria, and patients were divided into an equal number (n=2,422) of acupuncture and non-acupuncture groups, respectively, after 1:1 propensity-score matching. The dementia patients had a lower risk of disability development after acupuncture treatment than those who did not receive acupuncture treatment (adjusted hazard ratio 0.65, 95% confidence interval 0.60–0.70, p < 0.001). The results were independent of basic variables or comorbidities in the two cohorts. Patients who did not use anti-dementia agents had a lower risk of developing disability after receiving acupuncture intervention than those who used anti-dementia agents.

Conclusion: Our results revealed the relationship between acupuncture intervention and decreased risk of developing disability in dementia patients. The results are useful for dementia treatment, trial design and further planning of care programs.

Keywords: acupuncture, disability, dementia, traditional Chinese medicine

Introduction

Dementia is a neurodegenerative disease[1] and most patients are diagnosed at middle or old age. Additionally, some subtypes of dementia could be found at relatively young ages, such as frontotemporal dementia.[2] The primary clinical presentations of dementia patients vary, and delayed diagnosis is not uncommon.[2] The prevalence of dementia worldwide doubles every 5 years,[3] and it was estimated approximately 152.8 million cases will be identified in 2050.[4] According to the etiologies, dementia can be divided into several subgroups: Alzheimer's disease, vascular dementia and other dementia, including frontotemporal dementia and dementia with Lewy bodies, etc.[5] Alzheimer's disease is most commonly caused by mutant

proteins, such as tau and amyloid beta which accumulate in the human brain and subsequently cause memory loss and cognitive dysfunction. Vascular dementia is caused by cerebral vascular damage, and the symptoms of such a patient depend on the site and severity of the associated brain damage;[6] its relationship with Alzheimer's disease is still controversial.[7] Other dementia includes Lewy body disease and frontotemporal dementia, which are characterized by slow progression and relative memory preservation.[8]

The management of dementia could be divided into nonpharmacologic and pharmacologic approaches.[9] Trying to elevate activity through exercise and social interaction, keeping proper sleep and personal hygiene, and maintaining psychological health are considered nonpharmacologic managements.[8] Four types of medications that increase the acetylcholine concentration in the brain and decrease the effect of glutamate to relieve the course of dementia from Alzheimer's disease are available: donepezil, rivastigmine, galantamine, and memantine.[8] Donepezil, rivastigmine, and galantamine could be used for mild to moderate dementia, while memantine and donepezilI could be prescribed for moderate-to-severe dementia.[8] However, the response rates of these agents are not favorable, and complications including dizziness, gastrointestinal uncomfortable, insomnia, fatigue, abnormal cardiac conduction, and liver dysfunction have been reported.[10] Low motor function is the core mechanism of the aforementioned problems, and disability has been noted as a predictor of death.[11] Thus, the study of preventive interventions for decreasing dementia complications, including integrative treatments, is becoming an important topic. The atypical antipsychotics, such as risperidone and olanzapine may be beneficial for controlling neuropsychiatric symptoms, but they also increase the risk of stroke.[12]

Chinese medicine is an Eastern-style integrative intervention that usually involves the use of Chinese herbs and acupuncture.[13] A meta-analysis showed that acupuncture could potentially improve the Hasegawa Dementia Scale (HDS), Mini-Mental State Examination scores (MMSE), and Scale for the differentiation of syndromes of vascular dementia (SDSVD) in patients with vascular dementia.[14] Compared to those treated for Alzheimer's disease with Western medicine, patients in the acupuncture cohort were found to achieve preservation of their activities of daily living (ADL).[15] The above evidence was collected from clinical trials in which patients were observed for several months. However, studies assessing middle- to long-term outcomes after acupuncture intervention are still lacking.

Public health insurance has been practiced in Taiwan for 28 years, and data on the clinical care of clinics and admissions are recorded in a health insurance database called the National Health Insurance Research Database (NHIRD) as deidentified personal medical information. To date, more than 99% of Taiwanese individuals have been covered by the NHIRD.[13] In other words, the NHIRD is a large-scale, long-term follow-up healthcare database. All medical services from both Western and Chinese physicians are recorded in the NHIRD.[13] The aim of our study was to use the NHIRD to investigate the association between acupuncture therapy and the risk of disability development in patients with dementia, including subgroup analyses according to the etiologies of dementia. The results could offer information that could not be obtained from short-term clinical trials or laboratory experimental studies.

Materials and Methods
Study Design and Setting
This is a retrospective cohort study performed by 1:1 propensity-score matching. Data from patients who were newly diagnosed with dementia from 1 January 2008 to 31 December 2016 in the Longitudinal Generation Tracking Database 2005 (LGTD2005) were collected. The index date and immortal time were defined as the first time that patients received acupuncture treatment and the interval from dementia being diagnosed to the index date, respectively. Patients were followed up until December 31, 2017, or withdrawn from the LGTD2005.

Participants
The inclusion criterion was a diagnosis of dementia found in ≥ 2 medical records. The exclusion criteria were (1) lacking of basic patient characteristics, such as sex, age, urbanization or income level, and (3) interruption of health insurance coverage. The patients meeting our inclusion criteria were divided into acupuncture and non-acupuncture cohorts depending on whether they accepted acupuncture interventions from the date of diagnosis of dementia to 31 December 2016.

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Variables

The diagnosis of dementia was coded by the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM) codes: 290.0–290.4, 294.1, 331.0 to 331.2/F00, F01, F02, F03, and G30. The characteristics of the patients were sex, age, urbanization and income levels. There were 3 subgroups based on age: <64 years, 65–79 years, and ≥80 years. The definition of elderly individual in Taiwan is ≥65 years old[16] and those who are aged ≥80 years could apply whole-day caregiver without limitation due to the higher prevalence rate of disability found in this age interval.[17] The age had a high association with the disability which needs to conduct further subgroup analysis. Considering the convenience of medical visits in different areas and the affordability of medical expenses, we set urbanization and monthly income to be the variables, respectively. The level of urbanization was also divided into level 1 (highest) to level 3 (lowest).[18,19] The income of the patients could be designed as 3 levels: ≥New Taiwan dollar (NTD)40,000, NTD20,000–39,999, and ≤ NTD20,000.[20,21]

Comorbidities were defined by the ICD-9-CM and ICD-10-CM codes when they existed in the medical records ≥2 times before the date of dementia diagnosis, such as diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), obesity, cancer, stroke and Parkinson's disease (PD). Personal habits were also collected as smoking and alcoholism.

The anti-dementia agents are donepezil, rivastigmine, galantamine and memantine. According to the prescription guidelines, when patients used donepezil, rivastigmine and galantamine, they would be set as mild-to-moderate dementia. And patients were included in the moderate-to-severe dementia when they used memantine.[8] Based on the manipulation of acupuncture, the types of acupuncture were divided into 2 cohorts: manual acupuncture and electroacupuncture. The primary outcome was the measurement of disability, which was defined as the placement of a urinary catheter, nasogastric tube, and tracheostomy tube in dementia patients.[22]

Data Sources and Ethical Considerations

We used the Longitudinal Generation Tracking Database 2005, containing 2 million individual medical records randomly collected from the NHIRD, as our source. There was no identified personal information in the database we used, and informed consent was waived. This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taiwan (CMUH109-REC2-031(CR-3)).

Bias

To control for potential selection bias, propensity-score matching was used to minimize the difference between the acupuncture and non-acupuncture groups.

Statistical Methods

The chi-square test was used to calculate the difference in baseline characteristics between the acupuncture and non-acupuncture groups. The Kaplan–Meier method and the Log rank test were used to detect the difference in disability noted between the two groups. The crude hazard ratio (cHR) and adjusted hazard ratio (aHR) were predicted by Cox proportional hazard regression analysis. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform our analyses, and when P was < 0.05, the difference was considered to be significant.

Results

There were 25,924 patients that met our inclusion criteria, but disability was noted before dementia in 16,141 patients, and personal characteristics were missing in 23 patients. Finally, 9,760 newly diagnosed dementia patients were divided into acupuncture and non-acupuncture groups. Then, a 1:1 propensity-score match was performed, and 2,422 dementia patients were found in each group (Supplementary Figure 1). The distributions of sex, mean age, urbanization level, income level, comorbidities, habits, or medication use in the two groups were not significant after 1:1 propensity-score matching (Table 1). And the median income of the two cohorts is the same (NTD22,800).

Table I Characteristics of Patients with Dementia Who Received Acupuncture Therapy and Patients with Dementia Who Did Not Receive Acupuncture Therapy

Variable	Before PS Matching Acupuncture Intervention				p-value†	After PS Matching Acupuncture Intervention				p-value†
	No (n=7291)		Yes (n=2469)			No (n=2422)		Yes (n=2422)		
	n	%	n	%		n	%	n	%	
Sex					<0.001					0.953
Female	3990	54.73	1523	61.68		1486	61.35	1488	61.44	
Male	3301	45.27	946	38.32		936	38.65	934	38.56	
Age (year)					<0.001					<0.001
<64	245	3.36	178	7.21		194	8.01	138	5.70	
65–79	2993	41.05	1551	62.82		1404	57.97	1544	63.75	
≥80	4053	55.59	740	29.97		824	34.02	740	30.55	
Mean (SD)	79.9	8.52	74.98	8.38	<0.001	75.67	8.93	75.36	7.89	0.199
Urbanization level					0.115					0.703
I(highest)	3247	44.53	1159	46.94		1146	47.32	1135	46.86	
2	2856	39.17	925	37.46		918	37.90	908	37.49	
3(lowest)	1188	16.29	385	15.59		358	14.78	379	15.65	
Income Level					0.004					0.009
<NTD20,000	2689	36.88	918	37.18		869	35.88	904	37.32	
NTD20,000–39,999	3580	49.10	1143	46.29		1210	49.96	1115	46.04	
≧NTD40,000	1022	14.02	408	16.52		343	14.16	403	16.64	
Comorbidities										
DM	2984	40.93	1120	45.36	0.000	1112	45.91	1102	45.50	0.773
Hypertension	5886	80.73	1955	79.18	0.094	1947	80.39	1928	79.60	0.495
Hyperlipidemia	3853	52.85	1603	64.93	0.000	1595	65.85	1568	64.74	0.415
CVD	3719	51.01	1375	55.69	0.000	1393	57.51	1351	55.78	0.223
COPD	3375	46.29	1219	49.37	0.008	1187	49.01	1195	49.34	0.818
Obesity	76	1.04	30	1.22	0.474	19	0.78	28	1.16	0.187
Cancer	445	6.10	108	4.37	0.001	109	4.50	108	4.46	0.945
Stroke	3746	51.38	1331	53.91	0.030	1351	55.78	1300	53.67	0.141
Parkinson's disease	1080	14.81	403	16.32	0.071	396	16.35	396	16.35	1.000
Habits										
Smoking	90	1.23	40	1.62	0.148	40	1.65	38	1.57	0.819
Alcoholism	37	0.51	15	0.61	0.555	12	0.50	13	0.54	0.841
Medication										
For moderate to severe dementia										
Memantine	232	3.18	68	2.75	0.287	65	2.68	66	2.73	0.929
For mild to moderate dementia										
Galantamine	74	1.01	22	0.89	0.590	27	1.11	22	0.91	0.473
Rivastigmine	337	4.62	122	4.94	0.517	115	4.75	122	5.04	0.641
Donepezil	462	6.34	149	6.03	0.593	133	5.49	148	6.11	0.357

Notes: †Chi-square test, *t*-test.
Abbreviations: PS, propensity-score; SD, standard deviation; NTD, New Taiwan dollar; DM, diabetes mellitus; CVD, Cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

Dementia patients who accepted acupuncture therapy had a lower risk of developing disability than those who did not accept acupuncture therapy (aHR 0.65, 95% confidence interval (CI) 0.60–0.70, p < 0.001, Supplementary Figure 2). Table 2 shows the effect of each variable on the results from acupuncture intervention through the Cox model with HRs and 95% CIs. Male dementia patients had a higher risk of having disability than female individuals did (aHR 1.33, 95% CI 1.22–1.44). The age intervals of ≥80 years old (aHR 2.60, 95% CI 2.11–3.20) and 65–79 years old (aHR 1.52, 95% CI 1.24–1.87) had a higher risk of disability development than those aged <65 years. Compared to those living in

Table 2 Cox Model with Hazard Ratios and 95% Confidence Intervals of Disability Associated with Receiving Acupuncture and Covariates Among Patients with Dementia

Variable	Disability			Crude		Adjusted†	
	Event	PY	IR	HR (95% CI)	p-value	HR (95% CI)	p-value
Acupuncture intervention							
No	1246	6075	205.10	1.00 (reference)	-	1.00 (reference)	-
Yes	1097	8091	135.58	0.67 (0.62, 0.73)***	<0.001	0.65 (0.60, 0.70)***	<0.001
Sex							
Female	1294	9022	143.43	1.00 (reference)	-	1.00 (reference)	-
Male	1049	5144	203.92	1.42 (1.31, 1.54)***	<0.001	1.33 (1.22, 1.44)***	<0.001
Age (year)							
<64	103	1138	90.54	1.00 (reference)	-	1.00 (reference)	-
65–79	1290	9308	138.59	1.54 (1.26, 1.88)***	<0.001	1.52 (1.24, 1.87)***	<0.001
≥80	950	3721	255.33	2.81 (2.29, 3.45)***	<0.001	2.60 (2.11, 3.20)***	<0.001
Urbanization level							
1(highest)	1079	6644	162.40	1.00 (reference)	-	1.00 (reference)	-
2	922	5323	173.22	1.07 (0.98, 1.17)	0.1422	1.11 (1.01, 1.21)*	0.0255
3(lowest)	342	2199	155.50	0.96 (0.85, 1.09)	0.5202	0.99 (0.87, 1.11)	0.8329
Income Level							
<NTD20,000	900	5111	176.09	1.00 (reference)	-	1.00 (reference)	-
NTD20,000–39,999	1088	6750	161.19	0.92 (0.84, 1.00)*	0.0495	1.04 (0.95, 1.14)	0.3948
≧NTD40,000	355	2306	153.98	0.88 (0.78, 0.99)*	0.0358	0.97 (0.86, 1.10)	0.6719
Comorbidities							
DM							
No	1212	8027	150.99	1.00 (reference)	-	1.00 (reference)	-
Yes	1131	6139	184.22	1.22 (1.12, 1.32)***	<0.001	1.27 (1.16, 1.38)***	<0.001
Hypertension							
No	365	3176	114.93	1.00 (reference)	-	1.00 (reference)	-
Yes	1978	10,990	179.98	1.56 (1.39, 1.74)***	<0.001	1.31 (1.16, 1.47)***	<0.001
Hyperlipidemia							
No	907	4763	190.43	1.00 (reference)	-	1.00 (reference)	-
Yes	1436	9403	152.71	0.8 (0.74, 0.87)***	<0.001	0.74 (0.68, 0.81)***	<0.001
CVD							
No	966	6453	149.70	1.00 (reference)	-	1.00 (reference)	-
Yes	1377	7713	178.52	1.19 (1.09, 1.29)***	<0.001	1.00 (0.91, 1.09)	0.9225
COPD							
No	1125	7498	150.03	1.00 (reference)	-	1.00 (reference)	-
Yes	1218	6668	182.67	1.22 (1.12, 1.32)***	<0.001	1.04 (0.95, 1.13)	0.4184
Obesity					-		
No	2326	14,037	165.71	1.00 (reference)	-	1.00 (reference)	-
Yes	17	129	131.36	0.80 0 (0.49, 1.28)	0.3481	1.13 (0.7, 1.82)	0.6218
Cancer					-		
No	2223	13,631	163.08	1.00 (reference)	-	1.00 (reference)	-
Yes	120	535	224.41	1.37 (1.14, 1.65)***	<0.001	1.15 (0.95, 1.38)	0.1428
Stroke					-		
No	913	6855	133.18	1.00 (reference)	-	1.00 (reference)	-
Yes	1430	7311	195.60	1.46 (1.35, 1.59)***	<0.001	1.29 (1.18, 1.41)***	<0.001
Parkinson's disease					-		
No	1900	12,121	156.75	1.00 (reference)	-	1.00 (reference)	-
Yes	443	2045	216.61	1.37 (1.24, 1.52)***	<0.001	1.26 (1.14, 1.4)***	<0.001

(*Continued*)

Table 2 (Continued).

Variable	Disability			Crude		Adjusted†	
	Event	PY	IR	HR (95% CI)	p-value	HR (95% CI)	p-value
Medication							
For moderate to severe dementia							
Memantine							
No	2257	13,775	163.85	1.00 (reference)	-	1.00 (reference)	-
Yes	86	392	219.66	1.34 (1.08, 1.66)**	0.008	1.38 (1.1, 1.72)**	0.0048
For mild to moderate dementia							
Galantamine					-		
No	2313	14,011	165.08	1.00 (reference)	-	1.00 (reference)	-
Yes	30	155	193.45	1.18 (0.82, 1.69)	0.3737	1.13 (0.78, 1.62)	0.5241
Rivastigmine					-		
No	2217	13,435	165.02	1.00 (reference)	-	1.00 (reference)	-
Yes	126	732	172.24	1.05 (0.87, 1.25)	0.6259	1.11 (0.92, 1.33)	0.2699
Donepezil					-		
No	2207	13,264	166.38	1.00 (reference)	-	1.00 (reference)	-
Yes	136	902	150.83	0.91 (0.76, 1.08)	0.2777	0.89 (0.75, 1.06)	0.2052

Notes: †Adjusted HR: adjusted for age, sex, comorbidities and medications in Cox proportional hazards regression. *p-value < 0.05. **p-value < 0.01. ***p-value < 0.001.
Abbreviations: PY, Person-Year; IR, Incidence rate, per 1000 persons/years; HR, Hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; DM, diabetes mellitus; CVD, Cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

urbanization level 1, the patients living in level 2 (aHR 1.11, 95% CI 1.01–1.21) or level 3 (aHR 0.99, 95% CI 0.87–1.11) did not have a higher risk of becoming disabled. The risk of developing disability in subgroups of monthly income NTD20,000–39,999 or ≧NTD40,000 was not higher than <NTD20,000. Compared to patients who did not have DM (aHR 1.27, 95% CI 1.16–1.38), HTN (aHR 1.31, 95% CI 1.16–1.47), stroke (aHR 1.29, 95% CI 1.18–1.41), or PD (aHR 1.26, 95% CI 1.14–1.40), those who had comorbidities had a higher risk of disability. Hyperlipidemic patients had a lower risk of being diagnosed with disability than those who had this problem. The difference in disability development between patients who had or did not have CVD, COPD, obesity, or cancer was not significant. Whether anti-dementia agents, such as Witgen, Reminyl, Exelon, or Aricept, were used, they did not change the results of disability.

In the subgroup analyses, patients with all types of dementia had a lower risk of developing disability when they accepted acupuncture therapy than those who did not (Figure 1). Table 3 reveals that female (cHR 0.69, 95% CI 0.62–0.77; aHR 0.73, 95%
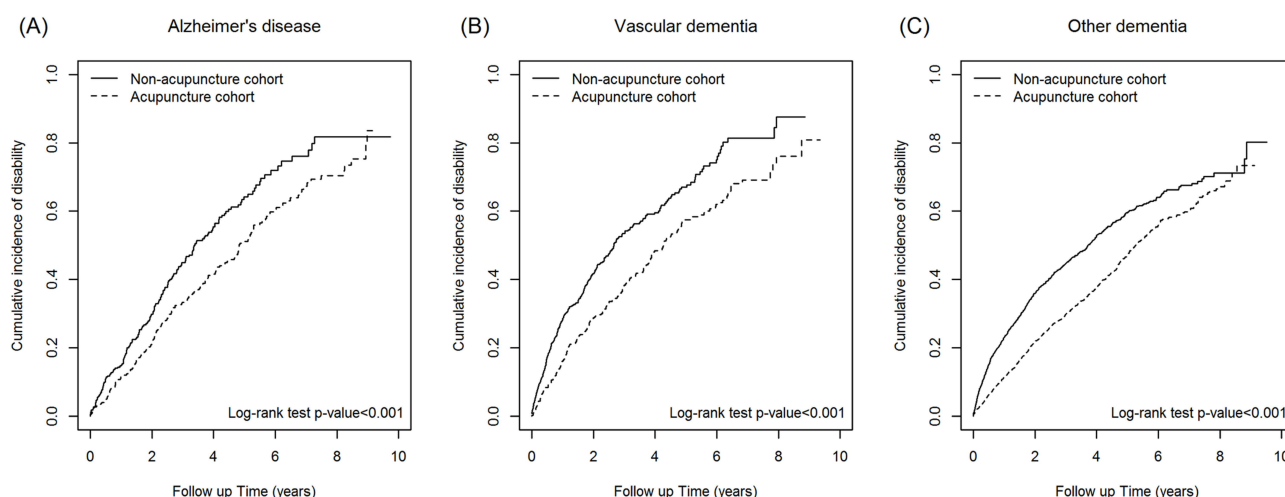

Figure 1 The difference of cumulative incidence of disability between acupuncture and non-acupuncture cohorts: (**A**) Alzheimer's disease, (**B**) vascular dementia, and (**C**) other dementia.

Table 3 Incidence Rates, Hazard Ratios and Confidence Intervals of Dementia Patients with Disability Who Received and Did Not Receive Acupuncture, Stratified by All Variables

Variable	Acupuncture						Crude		Adjusted[†]	
	No			Yes						
	Event	PY	IR	Event	PY	IR	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender										
Female	690	3966	173.97	604	5056	119.46	0.69 (0.62, 0.77)***	<0.001	0.73 (0.66, 0.82)***	<0.001
Male	556	2109	263.65	493	3035	162.43	0.63 (0.56, 0.71)***	<0.001	0.58 (0.51, 0.65)***	<0.001
Age (year)										
<64	65	567	114.67	38	571	66.57	0.60 (0.40, 0.89)*	0.017	0.62 (0.41, 0.93)*	0.022
65–79	655	3840	170.59	635	5468	116.13	0.68 (0.61, 0.76)***	<0.001	0.67 (0.60, 0.75)***	<0.001
≥80	526	1668	315.26	424	2052	206.61	0.66 (0.58, 0.75)***	<0.001	0.63 (0.55, 0.71)***	<0.001
Urbanization level										
1(highest)	577	2812	205.21	502	3832	130.99	0.65 (0.58, 0.73)***	<0.001	0.62 (0.55, 0.7)***	<0.001
2	487	2376	204.99	435	2947	147.61	0.72 (0.64, 0.82)***	<0.001	0.72 (0.63, 0.82)***	<0.001
3(lowest)	182	888	205.05	160	1312	121.97	0.60 (0.48, 0.74)***	<0.001	0.59 (0.47, 0.73)***	<0.001
Income Level										
<NTD20,000	477	2109	226.21	423	3002	140.90	0.63 (0.55, 0.71)***	<0.001	0.57 (0.50, 0.66)***	<0.001
NTD20,000–39,999	600	3034	197.73	488	3715	131.35	0.67 (0.6, 0.76)***	<0.001	0.69 (0.61, 0.78)***	<0.001
≧NTD40,000	169	932	181.34	186	1374	135.41	0.75 (0.61, 0.93)**	0.008	0.72 (0.58, 0.89)**	0.0024
Comorbidities										
DM										
No	640	3430	186.61	572	4597	124.42	0.67 (0.60, 0.75)***	<0.001	0.64 (0.57, 0.71)***	<0.001
Yes	606	2645	229.08	525	3494	150.26	0.66 (0.59, 0.75)***	<0.001	0.65 (0.58, 0.74)***	<0.001
Hypertension										
No	190	1307	145.35	175	1869	93.65	0.64 (0.52, 0.78)***	<0.001	0.60 (0.49, 0.75)***	<0.001
Yes	1056	4768	221.48	922	6223	148.17	0.68 (0.62, 0.74)***	<0.001	0.66 (0.6, 0.72)***	<0.001
Hyperlipidemia										
No	478	1921	248.86	429	2842	150.94	0.62 (0.55, 0.71)***	<0.001	0.57 (0.50, 0.65)***	<0.001
Yes	768	4154	184.87	668	5249	127.26	0.69 (0.62, 0.77)***	<0.001	0.70 (0.63, 0.78)***	<0.001
CVD										
No	488	2756	177.06	478	3697	129.31	0.73 (0.64, 0.83)***	<0.001	0.69 (0.60, 0.78)***	<0.001
Yes	758	3319	228.39	619	4394	140.86	0.63 (0.56, 0.70)***	<0.001	0.62 (0.56, 0.69)***	<0.001
COPD										
No	593	3222	184.05	532	4276	124.41	0.68 (0.61, 0.77)***	<0.001	0.67 (0.59, 0.75)***	<0.001
Yes	653	2853	228.88	565	3815	148.11	0.65 (0.58, 0.73)***	<0.001	0.64 (0.57, 0.71)***	<0.001
Obesity										
No	1238	6029	205.34	1088	8008	135.87	0.67 (0.62, 0.73)***	<0.001	0.65 (0.60, 0.70)***	<0.001
Yes	8	46	173.48	9	83	108.04	0.61 (0.24, 1.60)	0.3181	0.30 (0.07, 1.26)	0.1008
Cancer										
No	1181	5870	201.21	1042	7762	134.25	0.67 (0.62, 0.73)***	<0.001	0.66 (0.61, 0.72)***	<0.001
Yes	65	205	316.45	55	329	167.00	0.51 (0.36, 0.74)***	<0.001	0.47 (0.32, 0.70)***	<0.001
Stroke										
No	499	2896	172.33	414	3960	104.55	0.61 (0.53, 0.69)***	<0.001	0.61 (0.53, 0.69)***	<0.001
Yes	747	3179	234.95	683	4131	165.33	0.71 (0.64, 0.79)***	<0.001	0.68 (0.61, 0.76)***	<0.001
Parkinson's disease										
No	1006	5228	192.43	894	6893	129.70	0.68 (0.62, 0.75)***	<0.001	0.67 (0.61, 0.73)***	<0.001
Yes	240	847	283.33	203	1198	169.44	0.60 (0.50, 0.73)***	<0.001	0.58 (0.48, 0.70)***	<0.001
Medication										
For moderate to severe dementia										
Memantine										
No	1204	5897	204.17	1053	7877	133.67	0.66 (0.61, 0.72)***	<0.001	0.64 (0.59, 0.70)***	<0.001
Yes	42	178	236.14	44	214	205.94	0.88 (0.58, 1.36)	0.573	0.77 (0.49, 1.22)	0.267

(Continued)

Table 3 (Continued).

Variable	Acupuncture						Crude		Adjusted†	
	No			Yes						
	Event	PY	IR	Event	PY	IR	HR (95% CI)	p-value	HR (95% CI)	p-value
For mild to moderate dementia										
Galantamine										
No	1229	5996	204.96	1084	8015	135.25	0.67 (0.62, 0.72)***	<0.001	0.65 (0.60, 0.71)***	<0.001
Yes	17	79	216.09	13	76	170.13	0.63 (0.29, 1.36)	0.237	0.34 (0.12, 0.97)*	0.0431
Rivastigmine										
No	1188	5760	206.24	1029	7674	134.09	0.66 (0.61, 0.72)***	<0.001	0.64 (0.59, 0.70)***	<0.001
Yes	58	315	184.36	68	417	163.10	0.89 (0.62, 1.27)	0.513	0.88 (0.61, 1.27)	0.4886
Donepezil										
No	1178	5696	206.81	1029	7568	135.96	0.67 (0.61, 0.72)***	<0.001	0.65 (0.60, 0.71)***	<0.001
Yes	68	379	179.41	68	523	130.10	0.72 (0.51, 1.01)	0.058	0.69 (0.48, 0.98)*	0.037

Notes: †Adjusted HR: adjusted for age, sex, comorbidities and medications in Cox proportional hazards regression. *p-value < 0.05. **p-value < 0.01. ***p-value < 0.001.
Abbreviations: PY, Person-Year; IR, Incidence rate, per 1000 persons/years; HR, Hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; DM, diabetes mellitus; CVD, Cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

CI 0.66–0.82, Supplementary Figure 3A) and male (cHR 0.63, 95% CI 0.56–0.71; aHR 0.58, 95% CI 0.51–0.65, Supplementary Figure 3B) who accepted acupuncture had a lower risk of finding disability than those who did not. In all the age subgroups (<64-year-old (cHR 0.60, 95% CI 0.40–0.89; aHR 0.62, 95% CI 0.41–0.93, Supplementary Figure 4A), 65–79-year-old (cHR 0.68, 95% CI 0.61–0.76; aHR 0.67, 95% CI 0.60–0.75, Supplementary Figure 4B), and ≥80-year-old (cHR 0.66, 95% CI 0.58–0.75; aHR 0.63, 95% CI 0.55–0.71, Supplementary Figure 4C)), lower risks of having disability occurred after patients accepted acupuncture therapy, compared with those who did not accept acupuncture therapy. Lower risks of being diagnosed with disability after acupuncture treatment were noted at all levels of urbanization: level 1 (cHR 0.65, 95% CI 0.58–0.73; aHR 0.62, 95% CI 0.55–0.70), level 2 (cHR 0.72, 95% CI 0.64–0.82; aHR 0.72, 95% CI 0.63–0.82), and level 3 (cHR 0.60, 95% CI 0.48–0.74; aHR 0.59, 95% CI 0.47–0.73). Patients with all levels of monthly income had a lower risk of disability development when they started to receive acupuncture therapy: <NTD20,000 (cHR 0.63, 95% CI 0.55–0.71; aHR 0.57, 95% CI 0.50–0.66), NTD20,000–39,999 (cHR 0.67, 95% CI 0.60–0.76; aHR 0.69, 95% CI 0.61–0.78), and ≧NTD40,000 (cHR 0.75, 95% CI 0.61–0.93; aHR 0.72, 95% CI 0.58–0.74). Regardless of whether patients had comorbidities of DM (cHR 0.66, 95% CI 0.59–0.75; aHR 0.65, 95% CI 0.58–0.74), HTN (cHR 0.68, 95% CI 0.62–0.74; aHR 0.66, 95% CI 0.60–0.72), hyperlipidemia (cHR 0.69, 95% CI 0.62–0.77; aHR 0.70, 95% CI 0.63–0.78), CVD (cHR 0.63, 95% CI 0.56–0.70; aHR 0.62, 95% CI 0.56–0.69), COPD (cHR 0.65, 95% CI 0.56–0.70; aHR 0.64, 95% CI 0.57–0.71), cancer (cHR 0.51, 95% CI 0.36–0.74; aHR 0.47, 95% CI 0.32–0.70), stroke (cHR 0.71, 95% CI 0.64–0.79; aHR 0.68, 95% CI 0.61–0.76), PD (cHR 0.60, 95% CI 0.50–0.73; aHR 0.58, 95% CI 0.48–0.70) or not (DM (cHR 0.67, 95% CI 0.60–0.75; aHR 0.64, 95% CI 0.57–0.71), HTN (cHR 0.64, 95% CI 0.52–0.78; aHR 0.60, 95% CI 0.49–0.75), hyperlipidemia (cHR 0.62, 95% CI 0.55–0.71; aHR 0.57, 95% CI 0.50–0.65), CVD (cHR 0.73, 95% CI 0.64–0.83; aHR 0.69, 95% CI 0.60–0.78), COPD (cHR 0.68, 95% CI 0.61–0.77; aHR 0.67, 95% CI 0.59–0.75), stroke (cHR 0.61, 95% CI 0.53–0.69; aHR 0.61, 95% CI 0.53–0.69), PD (cHR 0.68, 95% CI 0.62–0.75; aHR 0.67, 95% CI 0.61–0.73)), their risk of being diagnosed with a disability were lower after acupuncture intervention than that of those who did not receive acupuncture therapy. When patients did not have obesity, the risk of disability development was lower (cHR 0.67, 95% CI 0.62–0.73; aHR 0.65, 95% CI 0.60–0.70) after they received acupuncture therapy than that of those who did not receive acupuncture therapy. When patients did not receive Western anti-dementia agents but received acupuncture therapy, their risks of disability were lower than those who received agents: no-Witgen (cHR 0.66, 95% CI 0.61–0.72; aHR 0.64, 95% CI 0.59–0.70), no-Reminyl (cHR 0.67, 95% CI 0.62–0.72; aHR 0.65, 95% CI 0.60–0.71), no-Exelon (cHR 0.66, 95% CI 0.61–0.72; aHR 0.64, 95% CI 0.59–0.70) or no-Aricept (cHR 0.67, 95% CI 0.61–0.72; aHR 0.65, 95% CI 0.60–0.71; Supplementary Figure 5). Supplementary Tables 1 and 2 showed that compared no-acupuncture users, the risks of disability is lower in the users accepted manual acupuncture (cHR 0.65, 95% CI 0.59–0.70; aHR 0.63, 95% CI 0.58–0.69), electroacupuncture (cHR 0.47, 95% CI 0.28–

0.79; aHR 0.51, 95% CI 0.30–0.87), and combination of manual acupuncture and electroacupuncture (cHR 0.61, 95% CI 0.51–0.73; aHR 0.61, 95% CI 0.51–0.72).

Discussion

Our results demonstrated that dementia patients could have a lower risk of disability as a result of acupuncture therapy. A significant relationship could be found in all the types of dementia. However, male sex, older age, and comorbidities, including DM, HTN, hyperlipidemia, stroke, and PD, were still risk factors contributing to a higher diagnosis of disability in dementia patients. From the results of subgroup analyses, most variable factors demonstrated their positive relationships with lowering the risk of disability after acupuncture treatment, except Western medication use.

The relationship between dementia and disability has been reported in longitudinal studies.[23,24] Males had a slightly higher risk (standardized rate ratio 1.41, 95% CI 1.12–1.76) of developing disability than females, which is similar to our findings.[23] Additionally, older dementia patients had a higher risk (OR 3.43, 95% CI 2.04–5.77) of having disability, which was shown in our participants.[23] Stroke has been noted as a confounding factor (OR 5.54, 95% CI 2.86–10.72) contributing to dementia, and we matched this disease before further analysis.[24] Although there was no significant relationship between CVD (OR 1.40, 95% CI 0.74–2.68) and dementia in a previous cohort study, we still controlled this variable factor for restricted results because CVD is still known as a potential risk factor.[24] Dementia is a cognitive impairment disorder since that the association between cognitive impairment and disability was observed in a meta-analysis (Hedges' $g = 0.76$, 95% CI 0.68–0.83).[25]

The possible mechanisms of dementia leading to disability could be divided into irreversible risk factors through biochemical pathways causing neurological, musculoskeletal, and systematic dysfunctions.[26] Sex, age, and genetic traits are irreversible factors, and chronic diseases (obesity, HTN, dyslipidemia, and DM), malnutrition (swallowing problem, inadequate diet), personal habits (smoking and alcoholism), psychosocial problems (insomnia, depression, stress, and less social activity), and sensory impairments (hearing and vision) are reversible factors. The biochemical pathways are activated by inflammatory processes, oxidative stress, genetic instability, and mitochondrial and telomere dysfunction. Problems such as neurodegenerative processes and neurosynaptic dysfunction, sarcopenia, frailty, and osteopenia are found in the neurological and musculoskeletal systems and cause systematic destruction. Most of the irreversible and reversible factors were controlled in our study by propensity-score matching to confirm that a reliable result was produced.

Several interventions have been used to prevent dementia from causing disability: supplementation, physical and cognitive training, and integrative care. Significant differences were found with physical and cognitive training only. Although integrative care is the mainstream intervention for sarcopenic and frail individuals, the lack of detailed diet or exercise suggestions to patients may cause nonsignificant results. The role of acupuncture in preventing disability may come from controlling reversible factors, such as reducing inflammation and increasing physical activity. A meta-analysis reported that acupuncture has the potential to control obesity (weighted mean difference (WMD) −0.47 kg/m2, 95% CI −0.58 to −0.35),[27] HTN (WMD −3.62 mmHg; 95% CI, −5.90 to −1.34),[28] dyslipidemia (SMD: −2.53, 95% CI: −4.55 to −0.67),[29] DM (−2.13 mmol/l, 95% CI −2.79 to −1.46),[30] dysphagia (SMD 2.02, 95% CI: 0.82 to 3.22),[31] smoking (relative risk 2.49, 95% CI 1.14 to 5.97),[32] insomnia (SMD 8.96, 95% CI 3.97 to 13.95),[33] depression (Hedges' $g = 0.76$, 95% CI 0.18 to 0.63),[34] stress (SMD −0.41, 95% CI −0.50 to −0.31),[35] hearing problems (RR = 2.36, 95% CI 1.20–4.67),[36] and vision dysfunction (SMD 0.18, 95% CI 0.17 to 0.20).[37] Acupuncture was also shown to control inflammation[36] and relieve oxidative stress[38] in animal models. Although dementia is more prevalent females,[39] the gender difference of disability is not obviously.[23] Based on our findings, screening and controlling risk factors contributing disability are the important measurements, especially when the male dementia patients visit Chinese physicians for acupuncture treatment.

There were several limitations in our study. Causality could not be obtained from a retrospective cohort study. The severity of disability could not be found or calculated from our database. However, when dementia patients need tube placement, they have poor physical function which cannot support them in maintaining daily activity.[22] The detailed prescription of acupuncture therapy was not recorded in our database. However, the main types of interventions, such as manual acupuncture, electroacupuncture and a combination of the two, could be identified and included in our variable factors. Biomarkers, images and cognitive tests could not be obtained from our database, but the formation of a diagnosis of dementia for insurance reimbursement in Taiwan would need the above information. The treatment dose of

acupuncture, such as the frequency, length of treatment or numbers of acupoints has not meet a uniform conclusion, thus we did not perform the analysis here. Not all the types of dementia could be analyzed in our study due to the limited samples in the real-world database.

Conclusion

The association between acupuncture treatment and the lower risk of disability development in dementia patients has been demonstrated in our results. These findings offer a possible long-term effect of acupuncture therapy in the dementia patients which is rarely found in the previous studies. Our study is useful for patients as well as researchers to design novel outcome measures, such as disability in dementia patients who would accept acupuncture therapy. It is helpful to confirm the role of acupuncture treatment in the dementia course.

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Disclosure

The authors report no conflicts of interest in this work.

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