

Acupuncture Treatment to Reduce the Risk of Dementia in Patients With Migraine: A Propensity Score–Matched Cohort Study

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Research article

Keywords: Acupuncture, Migraine, Dementia, National Health Insurance Research Database (NHIRD), propensity score, cohort

Posted Date: October 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-910563/v1>

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Abstract

Background

Migraine is a recurrent headache disease that has been identified as a risk factor for subsequent dementia. In Taiwan, some patients with migraine receive acupuncture treatment for other illnesses. Therefore, the association between the effects of acupuncture treatment and the risk of dementia in patients with migraine warrants investigation. The present study collected data from Taiwan's National Health Insurance Research Database (NHIRD) to investigate the incidence of dementia in patients with migraine who did and did not concurrently receive acupuncture treatment.

Methods

We conducted a retrospective matched-cohort study that included 37,266 patients, selected from the NHIRD, who were newly diagnosed with migraine at some time between 2000 and 2012. The follow-up period ranged from the index date (the date when patients first received acupuncture after their migraine diagnosis) to dementia diagnosis, withdrawal from the insurance program, or December 31, 2013. A 1:1 propensity score method was used to match an equal number of patients (N = 11,280) in the acupuncture and nonacupuncture cohorts based on sex, age, migraine diagnosis year, index year, insurance amount, urbanization level, baseline comorbidities, and medication usage. We employed Cox proportional hazards models to evaluate the risk of dementia. The cumulative incidence of dementia in both cohorts was estimated using the Kaplan–Meier method, and the difference was assessed through a log-rank test.

Results

Patients with migraine who received acupuncture treatment were found to have a lower risk of dementia (adjusted hazard ratio [aHR] = 0.48, 95% CI = 0.40–0.57) than those who did not undergo acupuncture treatment, after adjusting for age, sex, insurance amount, urbanization level, baseline comorbidities, and medication usage. The cumulative incidence of dementia was significantly lower in the acupuncture cohort than in the nonacupuncture cohort (log-rank test, $p < 0.001$).

Conclusions

This propensity score–matched cohort study demonstrated an association between acupuncture treatment and dementia development in patients with migraine in Taiwan. The results suggest that acupuncture treatment significantly reduced the development of dementia in patients with migraine. However, future study is required to provide more empirical evidence.

Background

Migraine is one of the most common neurological disorders; the newest edition (third) of the International Classification of Headache Disorders (ICHD-3) defines migraine as a recurrent headache disease, manifesting as a unilateral throbbing headache with moderate to severe pain intensity [1]. Common symptoms include headache and accompanying nausea, vomiting, photophobia, and occasional sensitivity to taste and sound [1]. According to a survey, the prevalence rate of migraine in the Taipei area for people over 15 years old is approximately 9.1%. Among this group, the prevalence rate is 4.5% for men and 14.4% for women [2]. In a study from the United States,

the prevalence of migraine was 8.6% in males, 17.5% in females, and 13.2% in the overall population; migraine exhibited a bimodal distribution in both sexes (peaking in those in late adolescence or their 20s and in those approximately 50 years of age) [3].

Several studies have indicated that migraine is associated with increased risks of stroke [4], depression [5], and dementia [6]. In addition, a cross-sectional prevalence study found that patients with migraine with and without aura are at increased risk for subclinical brain lesions [7]. Previous studies have revealed that silent brain lesions in the general population double the risk of dementia [8].

According to the 2019 Alzheimer's Disease International (ADI) Global Dementia Report, more than 50 million people worldwide are estimated to have dementia, and this number is expected to grow to 152 million by 2050 [9]. Dementia is a disease in which brain function is gradually lost. It not only leads to loss of memory but also adversely affects other cognitive functions, including language ability, spatial awareness, computing power, judgment, abstract thinking, and attention span. Acupuncture, traumatology manipulative therapies, and Chinese herbal products (CHPs) are all categorized as forms of traditional Chinese medicine (TCM), which is a popular form of alternative medicine in many countries [10]. Several studies have reported that acupuncture or CHPs are often used to treat migraine [11, 12]. A population-based cohort study indicated a decreased risk of dementia in patients with migraine who used CHPs [13]. However, this study investigated the effects of CHPs only, and the potential benefits of acupuncture as preventive treatment for dementia in patients with migraine are yet unknown.

The National Health Insurance Research Database (NHIRD) of Taiwan is used for health policy and management, disease treatment research, drug efficacy and disease risk factor analysis, real-time tracking of epidemics, and medical quality improvement. The National Health Insurance (NHI) program was launched in 1995, and by the end of 2010, more than 99% of people in Taiwan were enrolled in the program [14]. A previous study reported that middle-aged people in Taiwan are most likely to receive acupuncture treatment. Other research has revealed that patients most often receive acupuncture to treat physical injury and diseases of the musculoskeletal system and of connective tissue [15]. Another study found migraine to be associated with vascular risk factors and reduced cerebral blood flow (CBF) to be a potential cause of dementia [16]. One clinical trial indicated that CBF was enhanced through acupuncture [17]. In the present study, we hypothesized that acupuncture could reduce the risk of developing dementia among patients with migraine. Therefore, the association between acupuncture treatment and the risk of dementia was evaluated in 22,560 patients with migraine between 2000 and 2012 who were identified in the NHIRD.

Methods

Data source

The NHIRD, a large-scale health database in Taiwan, has enrolled over 99% of the population of Taiwan. The database contains data on outpatient visits, hospitalizations, medical treatments, and other medical services at each hospital visit.

We conducted the analyses by Longitudinal Health Insurance Database 2000 (LHID 2000), which is a subset of the NHIRD containing 1 million individuals randomly selected from the NHIRD; that the distribution of age and sex is similar to the original database after sampling has been confirmed. For personal information protection, patient identification numbers are encrypted before being released for use.

Each diagnosis was coded based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan [CMUH104-REC2-115(CR-6)].

Study population

This study included patients with migraine who had at least two outpatient visits or one hospitalization for migraine (*ICD-9-CM: 346*). Included patients were then classified into the acupuncture cohort or nonacupuncture-treated cohort.

The index date was set as the date when patients first received acupuncture treatment, and patients were followed until they were newly diagnosed as having dementia (*ICD-9-CM: 290, 294.1, 331.0*; at least two outpatient visits or one hospitalization), withdrew from the NHIRD, or December 31, 2013.

Migraine patients who were diagnosed with dementia before the index date, who were younger than 20 years old, or who were missing demographic information were excluded from this study. Each acupuncture-treated patient was matched with a nonacupuncture-treated patient through propensity score matching. The matching variables included age, sex, insurance amount, urbanization level, baseline comorbidities, and medication usage (Fig. 1).

Baseline comorbidity was defined as a comorbidity present before the index date and coded in the patient's medical records for at least two outpatient visits or one hospitalization. Included diseases were diabetes mellitus (*ICD-9-CM: 250*), hypertension (*ICD-9-CM: 401–405*), hyperlipidemia (*ICD-9-CM: 272*), coronary artery disease (*ICD-9-CM: 410–414*), head injury (*ICD-9-CM: 850–854, 959.01*), chronic kidney disease (*ICD-9-CM: 403–404, 585–589*), stroke (*ICD-9-CM: 430–438*), and depression (*ICD-9-CM: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311*). *Medication usage* was defined as the first prescribed medication after migraine and included sumatriptan, rizatriptan, ergotamine, naproxen, diclofenac, caffeine, acetaminophen, etoricoxib, celecoxib, and ibuprofen. Patient medication usage was classified into groups taking 0, 1, 2, or 3 + medications.

Statistical analysis

The differences between categorical and continuous variables of the two cohorts were tested using the chi-square test and *t* test, respectively.

The association between acupuncture treatment and the risk of dementia among patients with migraine was evaluated using the Cox proportional hazards model, and hazard ratios (HR), adjusted hazard ratios (aHR), and 95% CIs were employed to estimate the risk of dementia. The incidence rate of dementia was expressed as the number of diagnoses per 1,000 person-year. The Kaplan–Meier method was applied to create cumulative incidence curves for the acupuncture-treated and nonacupuncture-treated groups. The difference between two incidence curves was determined using a log-rank test. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). The cumulative incidence curve was plotted using R software. A two-sided *p*-value < 0.05 indicated statistical significance.

Results

Of the 11,280 patients with migraine who received acupuncture treatment, 73% were female and the overall mean age was 46 years (Table 1). The distributions of sex, age, insurance amount, and comorbidities exhibited

nonsignificant differences between the groups ($p > 0.05$). Patients who received acupuncture treatment lived in more urbanized areas ($p = 0.005$) and exhibited a higher rate of medication usage for migraine ($p = 0.031$).

Table 1
 Characteristics of newly diagnosed patients with migraine who did or did not receive acupuncture

Variable	Accepted acupuncture		<i>p</i> value
	No (n = 11280)	Yes (n = 11280)	
	n (%) / Mean (SD)	n (%) / Mean (SD)	
Sex			0.893
Women	8197 (72.7)	8206 (72.7)	
Men	3083 (27.3)	3074 (27.3)	
Age at baseline			
20–39	4363 (38.7)	4143 (36.7)	
40–65	5323 (47.2)	5724 (50.7)	
> 65	1594 (14.1)	1413 (12.5)	
Mean ± SD (years) ^b	46.4 (15.8)	46.3 (14.8)	0.621
Insurance amount (NT\$)			0.175
0-15840	5293 (46.9)	5299 (47)	
15841–28800	4456 (39.5)	4432 (39.3)	
28801–45800	1093 (9.7)	1160 (10.3)	
> 45800	438 (3.9)	389 (3.4)	
Urbanization^c			0.005
1 (highest)	3244 (28.8)	3308 (29.3)	
2	3535 (31.3)	3392 (30.1)	
3	1769 (15.7)	1939 (17.2)	
4 (lowest)	2732 (24.2)	2641 (23.4)	
Baseline Comorbidity			
Diabetes mellitus	1710 (15.2)	1699 (15.1)	0.838
Hypertension	3534 (31.3)	3513 (31.1)	0.763
Hyperlipidemia	3135 (27.8)	3133 (27.8)	0.976
Coronary artery disease	2206 (19.6)	2193 (19.4)	0.827
Head injury	1203 (10.7)	1203 (10.7)	1.000
Depression	1879 (16.7)	1875 (16.6)	0.943
Stroke	1426 (12.6)	1382 (12.3)	0.375

Variable	Accepted acupuncture		<i>p</i> value
	No (n = 11280)	Yes (n = 11280)	
	n (%) / Mean (SD)	n (%) / Mean (SD)	
Chronic kidney disease	1274 (11.3)	1272 (11.3)	0.966
Medications^d			0.031
0	7546 (66.9)	7431 (65.9)	
1	2802 (24.8)	2948 (26.1)	
2	742 (6.6)	749 (6.6)	
≥ 3	190 (1.7)	152 (1.3)	
Duration between migraine date and index, days	1147.7 (989.0)	1140.3 (1079.7)	0.595
Types of acupuncture, n(%)			
Manual acupuncture of TCM type	-	9780 (86.7)	
Electroacupuncture	-	353 (3.1)	
Combination of manual acupuncture and electroacupuncture	-	1147 (10.2)	
Acupuncture visits, times	-	8.3 (18.1)	
^a Chi-square test			
^b <i>t</i> test			
^c Urbanization was categorized into four levels according to the population density of the residential areas, with level 1 being the most urbanized and level 4 being the least urbanized			
^d Medications included: sumatriptan, rizatriptan, ergotamine, naproxen, diclofenac, caffeine, acetaminophen, etoricoxib, celecoxib, and ibuprofen			

The mean duration of the period between the date of migraine diagnosis and the index date was more than 3 years with no significant difference between the acupuncture and nonacupuncture groups ($p = 0.595$). Most acupuncture treatments were manual acupuncture treatments (86.7%).

Table 2 lists the potential risk factors for dementia among patients with migraine. Patients who accepted acupuncture treatment (aHR = 0.48, 95% CI = 0.40–0.57) who resided in a relatively less urbanized area (aHR = 0.62, 95% CI = 0.46–0.82) exhibited a significantly lower risk of dementia. Patients with relatively older ages, hypertension (aHR = 1.27, 95% CI = 1.02–1.59), stroke (aHR = 1.47, 95% CI = 1.24–1.76), and depression (aHR = 1.68, 95% CI = 1.40–2.02) and who used one type of migraine-related medication (aHR = 1.27, 95% CI = 1.06–1.51) exhibited a significantly higher risk of dementia after adjustment for demographics, baseline comorbidities, and medication usage.

Table 2

Cox model with hazard ratios and 95% confidence intervals of dementia associated with receiving acupuncture treatment and covariates among patients with migraine

Variable	No. of event (n = 623)	Crude		Adjusted	
		HR ^a (95%CI)	P-value	HR ^b (95%CI)	P-value
Accepted acupuncture					
No	425	Ref.		Ref.	
Yes	198	0.43(0.36–0.51)	< 0.001	0.48(0.40–0.57)	< 0.001
Sex					
Women	409	Ref.		Ref.	
Men	214	1.33(1.13–1.57)	< 0.001	0.93(0.79–1.11)	0.431
Age group					
20–39	5	Ref.		Ref.	
40–65	157	24.17(9.92–58.86)	< 0.001	20.12(8.18–49.50)	< 0.001
> 65	461	288.78(119.66–696.95)	< 0.001	133.92(54.17–331.12)	< 0.001
Insurance amount (NT\$)					
0-15840	234	Ref.		Ref.	
15841–28800	346	1.62(1.37–1.91)	< 0.001	1.05(0.88–1.26)	0.594
28801–45800	36	0.67(0.47–0.95)	0.025	0.91(0.64–1.31)	0.624
>45800	7	0.37(0.17–0.78)	0.009	0.58(0.27–1.24)	0.162
Urbanization					
1 (highest)	154	Ref.		Ref.	
2	180	1.08(0.87–1.34)	0.491	0.96(0.78–1.20)	0.745
3	69	0.75(0.57–1)	0.049	0.62(0.46–0.82)	0.001
4 (lowest)	220	1.61(1.31–1.97)	< 0.001	0.90(0.72–1.13)	0.354
Baseline Comorbidity (ref = nonsite comorbidity)					

Variable	No. of event (n = 623)	Crude		Adjusted	
		HR ^a (95%CI)	P-value	HR ^b (95%CI)	P-value
Diabetes mellitus	258	4.20(3.58–4.93)	< 0.001	1.16(0.98–1.39)	0.091
Hypertension	493	8.62(7.10-10.45)	< 0.001	1.27(1.02–1.59)	0.033
Hyperlipidemia	337	3.31(2.83–3.88)	< 0.001	0.96(0.80–1.14)	0.620
Coronary artery disease	376	6.54(5.57–7.67)	< 0.001	1.08(0.89–1.30)	0.433
Head injury	99	1.78(1.43–2.20)	< 0.001	1.17(0.94–1.45)	0.168
Depression	170	2.10(1.76–2.51)	< 0.001	1.68(1.40–2.02)	< 0.001
Stroke	297	6.85(5.86–8.02)	< 0.001	1.47(1.24–1.76)	< 0.001
Chronic kidney disease	192	3.68(3.10–4.36)	< 0.001	1.20(1.01–1.44)	0.041
Medications					
0	269	Ref.		Ref.	
1	239	1.81(1.52–2.15)	< 0.001	1.27(1.06–1.51)	0.009
2	89	2.17(1.70–2.76)	< 0.001	1.08(0.85–1.38)	0.531
≥ 3	26	2.41(1.60–3.61)	< 0.001	1.10(0.73–1.66)	0.634
<p>Crude HR ^a represents relative hazard ratio;</p> <p>Adjusted HR ^b represents adjusted hazard ratio: mutually adjusted for receiving acupuncture, age, sex, insurance amount, urbanization level, all comorbidities, and medication usage in Cox proportional hazards regression</p>					

Table 3 displays the diagnosis distribution for patients who received acupuncture treatment. Most received treatment because of injury or poisoning (70.1%) or receiving a diagnosis of a disease of the musculoskeletal system or connective tissue (64.8%).

Table 3
Distribution of acupuncture cohort by disease category or diagnosis in patients with migraine

Disease (ICD-9-CM)	Acupuncture users
	(n = 11280)
	n (%)
Infectious and parasitic disease (001-139)	27 (0.2)
Neoplasms (140-239)	39 (0.3)
Malignant(140-208)	24 (0.2)
Benign (210-229)	16 (0.1)
Endocrine, nutritional and metabolic disease and immunity disorder (240-279)	64 (0.6)
Blood and blood-forming organs (280-289)	19 (0.2)
Mental disorder (290-319)	118 (1)
Nervous system (320-389)	967 (8.6)
Circulatory system (390-459)	220 (2)
Respiratory system (460-519)	491 (4.4)
Digestive system (520-579)	626 (5.5)
Genitourinary system (580-629)	277 (2.5)
Complications of pregnancy, childbirth and the puerperium (630-676)	2 (0)
Skin and subcutaneous tissue (680-709)	106 (0.9)
Musculoskeletal system and connective tissue (710-739)	7305 (64.8)
Congenital anomalies (740-759)	42 (0.4)
Certain conditions originating in the perinatal period (760-779)	1 (0)
Symptoms, signs and ill-defined conditions (780-799)	1449 (12.8)
Injury and poisoning (800-999)	7904 (70.1)

Several stratified analyses were conducted to verify the associations (Table 4). Patients who received acupuncture treatment exhibited a decreased risk of dementia; this was true for women (aHR = 0.47, 95% CI = 0.38-0.58); men (aHR = 0.50, 95% CI = 0.38-0.67); patients aged 40 to 65 years (aHR = 0.43, 95% CI = 0.31-0.61); patients aged over 65 years (aHR = 0.44, 95% CI = 0.36-0.54); patients with diabetes (aHR = 0.52, 95% CI = 0.40-0.68), hypertension (aHR = 0.51, 95% CI = 0.42-0.61), hyperlipidemia (aHR = 0.50, 95% CI = 0.40-0.63), coronary artery disease (aHR = 0.47, 95% CI = 0.38-0.58), depression (aHR = 0.51, 95% CI = 0.37-0.71), stroke (aHR = 0.56, 95% CI = 0.44-0.71), or chronic kidney disease (aHR = 0.54, 95% CI = 0.40-0.73); and patients with or without migraine-related medication usage (aHR = 0.59, 95% CI = 0.46-0.76).

Table 4. Incidence rates, hazard ratios, and confidence intervals of dementia for patients with migraine who did and did not receive acupuncture in different stratifications

Variables	Accepted acupuncture						Compared with non-acupuncture users	
	No			Yes			Crude HR (95%CI)	Adjusted HR ^a (95%CI)
	(n=11280)			(n=11280)				
Event	Person years	IR [†]	Event	Person years	IR [†]			
Total	425	51892	8.19	198	56798	3.49	0.43(0.36-0.51) ^{***}	0.48(0.40-0.57) ^{***}
Sex								
Women	281	37082	7.58	128	40859	3.13	0.41(0.34-0.51) ^{***}	0.47(0.38-0.58) ^{***}
Men	144	14810	9.72	70	15940	4.39	0.45(0.34-0.6) ^{***}	0.5(0.38-0.67) ^{***}
Age group								
20-39	3	20493	0.15	2	21023	0.10	0.67(0.11-4.01)	0.46(0.07-2.97)
40-65	104	24878	4.18	53	29051	1.82	0.43(0.31-0.6) ^{***}	0.43(0.31-0.61) ^{***}
>65	318	6521	48.77	143	6724	21.27	0.44(0.36-0.54) ^{***}	0.44(0.36-0.54) ^{***}
Insurance amount (NT\$)								
0-15840	154	23285	6.61	80	25446	3.14	0.48(0.36-0.62) ^{***}	0.46(0.35-0.61) ^{***}
15841-28800	242	21346	11.34	104	23386	4.45	0.39(0.31-0.5) ^{***}	0.5(0.4-0.63) ^{***}
28801-45800	25	5246	4.77	11	6007	1.83	0.39(0.19-0.8) ^{**}	0.31(0.15-0.64) ^{**}
>45800	4	2015	1.99	3	1959	1.53	0.77(0.17-3.43)	0.63(0.13-3.1)
Urbanization								
1 (highest)	101	14253	7.09	53	16132	3.29	0.46(0.33-0.65) ^{***}	0.4(0.29-0.56) ^{***}
2	124	16165	7.67	56	16812	3.33	0.44(0.32-0.6) ^{***}	0.49(0.35-0.67) ^{***}
3	40	8411	4.76	29	9755	2.97	0.63(0.39-1.01)	0.69(0.42-1.13)
4 (lowest)	160	13063	12.25	60	14100	4.26	0.35(0.26-0.47) ^{***}	0.47(0.35-0.64) ^{***}

Baseline Comorbidity (ref=nonsite comorbidity)								
Diabetes mellitus	171	7354	23.25	87	8292	10.49	0.45(0.35-0.59)***	0.52(0.4-0.68)***
Hypertension	332	15792	21.02	161	17417	9.24	0.44(0.37-0.53)***	0.51(0.42-0.61)***
Hyperlipidemia	222	13538	16.40	115	14959	7.69	0.47(0.37-0.59)***	0.5(0.4-0.63)***
Coronary artery disease	257	9662	26.60	119	10879	10.94	0.41(0.33-0.51)***	0.47(0.38-0.58)***
Head injury	58	4978	11.65	41	5424	7.56	0.65(0.44-0.97)*	0.85(0.56-1.28)
Depression	116	7951	14.59	54	8476	6.37	0.44(0.32-0.61)***	0.51(0.37-0.71)***
Stroke	194	6032	32.16	103	6700	15.37	0.48(0.38-0.61)***	0.56(0.44-0.71)***
Chronic kidney disease	123	5393	22.81	69	6343	10.88	0.48(0.36-0.64)***	0.54(0.4-0.73)***
Medications								
0	177	30432	5.82	92	33204	2.77	0.48(0.37-0.62)***	0.59(0.46-0.76)***
1	158	15125	10.45	81	17042	4.75	0.46(0.35-0.6)***	0.46(0.35-0.61)***
2	67	4906	13.66	22	5264	4.18	0.31(0.19-0.5)***	0.35(0.21-0.57)***
≥3	23	1428	16.11	3	1288	2.33	0.15(0.05-0.5)**	0.11(0.03-0.39)***

Abbreviation: IR, incidence rate per 1,000 person-years; HR, hazard ratio; CI, confidence interval

Adjusted HR^a represented adjusted hazard ratio: mutually adjusted for receiving acupuncture, age, sex, insurance amount, urbanization level, all comorbidities, and medication usage in Cox proportional hazards regression

*:<0.05; **:<0.01; *** $p < 0.001$

Figure 2 illustrates the significantly lower incidence of dementia in patients with migraine who underwent acupuncture treatment compared with their nonacupuncture counterparts ($p < 0.001$).

Discussion

The results of the present study indicated that the incidence of dementia was 52% lower among patients with migraine who received acupuncture treatment than among those who did not receive acupuncture treatment. This suggests that acupuncture treatment may decrease the risk of dementia in patients with migraine. After multiple

adjustments for sex, age, insurance amount, urbanization level, baseline comorbidities, and medication usage, acupuncture treatment was found to play a key role in reducing the risk of dementia. Previous studies have reported that acupuncture can exert preventive effects in populations with several diseases associated with dementia, including traumatic brain injury (TBI) [18], stroke [19], and hypertension [20]. From this, we inferred that acupuncture may also prevent dementia; for this reason, we conducted this study.

The present study indicated that the risk of dementia increases with advancing age. Patients with migraine who were aged 40–65 years had a 20.12-fold higher risk of dementia than younger individuals, whereas the risk increased to 133.92-fold for those aged over 65 years, after adjusting for age, sex, and baseline comorbidities. The risk of developing dementia after age 60 was higher among individuals with migraine in midlife than among individuals without [21]. Therefore, aging can be identified as a key factor that increases the incidence of dementia [22].

Of all the baseline comorbidities associated with migraine, hypertension, depression, and stroke were found to significantly increase the risk of dementia the most. In previous study, patients at midlife ages with high blood pressure were found to have a higher risk of cognitive decline, including Alzheimer's disease and dementia [23]. Early life depressive symptoms have been revealed to be related to a 2-fold or greater increase in the risk of dementia [24]. In addition, studies on stroke have revealed that vascular risk factors may also be independent risk factors for developing dementia [25]. In this study, acupuncture was found to potentially reduce the incidence of dementia in patients with hypertension, depression, and stroke.

In the current study, patients with migraine who received acupuncture treatment were divided into two groups: those affected by musculoskeletal system or connective tissue disorders (64.8%) and those affected by injury or poisoning (70.1%). Injury and disorders of the musculoskeletal system or connective tissue were the predominant reasons for patients to seek acupuncture treatment [15]. A previous study indicated that patients with migraine exhibited significantly more musculoskeletal dysfunction than migraine-free control participants [26]. Most patients had cervical musculoskeletal impairments that accompanied their migraine episodes [27, 28]. Acupuncture is a safe form of intervention and is a feasible option for patients with chronic neck pain [29].

A population-based database study indicated that TBI is a risk factor for migraine [30]. Acupuncture functions as a neuroprotector because it promotes the recovery of the neuronal deficit resulting from TBI by activating the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB) signaling pathway at specific acupoints (Baihui, Renzhong, Hegu, and Zusanli) [31]. Combining acupuncture with a TBI treatment regimen was reported to reduce the risk of dementia by 35% [18]. Therefore, acupuncture can not only reduce TBI symptoms but also prevent subsequent dementia.

An increased risk of dementia caused by migraine can be attributed to several mechanisms such as cerebral hypoperfusion, white matter hyperintensities (WMHs), stress, and depression [32–35]. A case report demonstrated that headache was associated with bilateral hypoperfusion starting from the occipital lobes and spreading anteriorly to the temporal and parietal lobes, providing clear evidence of the spreading depression associated with spontaneous migraine [36]. Olesen et al. [37], after observing changes in CBF, proposed that the mechanism of migraine-induced cerebral ischemia is spreading cortical depression. However, this proposition related only to migraines with aura. Another study found that, because changes in the brain indicated that cerebral small vessel disease increases the risk of most dementia types and cerebrovascular dysfunction, the vascular factors of migraine may be related to the risk of dementia [21]. Yet another study determined that acupuncture at the Buihui

(GV20) and Yintang (GV29) points increased the CBF of the prefrontal lobe and hippocampus in mouse models of Alzheimer's disease [38]. Moreover, a pilot study demonstrated a significant increase in CBF after true acupuncture in patients with stroke [17]. Together, the results of these studies indicate that acupuncture may reduce the risk of dementia in patients with migraine, possibly by increasing CBF.

WMHs in the brain are frequently discovered on MRI scans in older people [34] and are associated with migraine [39]. High-resolution evidence has indicated that WMHs give rise to cognitive impairment and play a crucial role in the development of dementia [34, 8]. Acupuncture at the Buihui (GV20) and Zusanli (ST36) points has been found to prevent cognitive function decline in rat models of vascular dementia by ameliorating white matter perfusion and maintaining its integrity [40]. In addition, acupuncture at the Yanglingquan (GB34) point was found to potentially enhance the communication between cortices with damaged white matter tracts in patients with ischemic stroke [41]. Therefore, we infer that acupuncture modulates these alterations of white matter, thereby preventing the development of dementia.

Stress, which affects the hypothalamus–pituitary–adrenal (HPA) system, may also contribute to dementia [42, 33]. Chronic stress has been found to enhance an individual's susceptibility to inflammatory activities in the brain, which affects dementia risk by increasing inflammatory cytokines such as interleukin (IL)-1 β , IL-6, tumor necrosis factor- α (TNF- α), or interferon- γ (INF- γ) [33]. Oxidative stress, which induces excessive production of free radical species, could lead to oxidative biomolecules and expedite aging [43]. Electroacupuncture (EA) was found to decrease the serum levels of IL-1 β , IL-6, and TNF- α in a rat model of migraine [44]. In addition, acupuncture was found to attenuate cognitive impairment and neuronal death by downregulating hippocampal thioredoxin-interaction proteins (TXNIPs) to inhibit oxidative stress and inflammation in a rat model of vascular dementia [45]. These studies illustrate the potential of acupuncture to protect against dementia. However, further investigation is required to determine whether these mechanisms are applicable to humans.

A national cohort study indicated that severe depression also increased the risk of dementia, with some patients being diagnosed with dementia two decades after their depressive episode [32]. Several mechanisms may link depression and dementia, including 1) vascular disease, 2) increased deposition of β -amyloid, and 3) inflammatory changes [24]. Acupuncture has been identified as having potential to enhance CBF in both animals and humans [38, 17]. Moreover, manual acupuncture or EA at specific acupoints has been found to improve cognitive impairment and suppress the generation of amyloid beta ($A\beta$) in several rat models of AD [46]. Acupuncture also significantly decreased the serum levels of IL-1 β , IL-6, and TNF- α in a chronic stress model of depression in rats [47]. Acupuncture, through multiple depression-associated pathways, could therefore reduce the risk of dementia in patients with migraine by increasing CBF, decreasing $A\beta$ generation, and decreasing the contents of proinflammatory cytokines in the brain.

The present study leaves open one key question: the mean number of acupuncture visits was only 8.3 during the study period, which may not be enough to prevent the development of dementia (Table 1). However, compared with standard pharmacological agents, acupuncture is a safe and beneficial treatment for chronic migraine [48]. Acupuncture not only decreases migraine recurrence for an extended period but also reduces the need for rescue medication [49]. Therefore, acupuncture may be used to improve the quality of life of and increase physical activity in patients with migraine. Moderate-intensity physical exercise, such as aerobic activity, is often prescribed as a means of decreasing cognitive impairment and reducing the risk of dementia by attenuating the progression of neurodegenerative processes and age-related loss of synapses and neuropil [50]. Notably, no more

than 15 visits for acupuncture treatment are covered through Taiwan's NHI program per month. Patients may have received additional, self-paid acupuncture treatments. However, these treatments are not included in the NHIRD and were, therefore, not included in this study.

The present study had other limitations that should be addressed. First, the NHIRD does not indicate the severity and duration of migraine. Accordingly, we performed 1:1 propensity score matching, which was useful in minimizing the difference between the two cohorts. Second, information regarding several aspects of treatment is not recorded in the NHIRD, including the acupoints used and the frequency and duration of treatment. Therefore, we were unable to clearly identify which acupoints may treat both migraine and dementia. Third, the NHIRD does not contain laboratory data or brain images; therefore, no empirical evidence could be evaluated to understand the mechanism through which acupuncture reduces the incidence of dementia in patients with migraine. Fourth, because some cases of dementia are late onset, the duration of the current study's follow-up period was insufficient to capture these. Double-blind, randomized clinical trials are required in the future.

Conclusions

The results of the present study indicate that the incidence of dementia was lower among patients with migraine who received acupuncture treatment than among patients with migraine who did not, suggesting that acupuncture may reduce the development of dementia. This is mediated through several pathways, including the modulation of CBF, WMHs, stress, and depression. Our study emphasizes the need for clinical trials that include laboratory data and brain imaging to identify potential preventive mechanisms.

Abbreviations

ICHD-3: International Classification of Headache Disorders, Third Edition

ADI: Alzheimer's Disease International

CHPs: Chinese herbal products

TCM: Traditional Chinese medicine

NHIRD: National Health Insurance Research Database

NHI: National Health Insurance

CBF: Cerebral blood flow

LHID 2000: Longitudinal Health Insurance Database 2000

ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification

HR: Hazard ratio

aHR: Adjusted hazard ratio

CIs: Confidence intervals

TBI: Traumatic brain injury

AD: Alzheimer's disease

BDNF: Brain-derived neurotrophic factor

TrkB: Tropomyosin receptor kinase B

WMHs: White matter hyperintensities

HPA: Hypothalamus–pituitary–adrenal

IL: Interleukin

TNF- α : Tumor necrosis factor- α

INF- γ : Interferon- γ

TXNIP: Thioredoxin-interaction protein

A β : Amyloid beta

Declarations

Authors' contributions

CHH conceptualized this study. MCL performed the statistical analyses. CHH, CLH, and ICC contributed to the interpretation of the acupuncture data. MCL, CHH, and ICC contributed to the interpretation of the statistical data. CHH drafted the manuscript. CHH, CLH, and ICC finalized the manuscript. Thus, all authors in this study have contributed to the work and have approved the manuscript for submission.

Funding

This study was supported in part by China Medical University Hospital (DMR-107-008), Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), Multi-arm Optimization of Stroke Thrombolysis (MOST) Clinical Trial Consortium for Stroke (MOST 109-2321-B-039-002), and the Tseng-Lien Lin Foundation in Taichung, Taiwan. The study also was financially supported by the Chinese Medicine Research Center of China Medical University as part of the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education in Taiwan (**CMRC-CENTER-0**). The funders did not participate in carrying out the study.

Availability of data and material

Data are available from the National Health Insurance Research Database (NHIRD), published by the Taiwan National Health Insurance (NHI) Bureau. The use of the NHIRD is limited to research purposes only. Due to the legal restrictions imposed by the government of Taiwan in relation to the Personal Information Protection Act, the data used for this study cannot be made publicly available. Request for data can be sent as a formal proposal to the NHIRD (<http://nhird.nhri.org.tw>).

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study [CMUH104-REC2-115(CR-6)].

Consent for publication

Not applicable.

Acknowledgments

This study was conducted using data from the NHIRD, which was provided by the National Health Insurance Administration and the Ministry of Health and Welfare, and supervised by the National Health Research Institutes. We would like to thank the management of the office for health data of China Medical University Hospital for collecting and analyzing the data used in this study.

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Figures

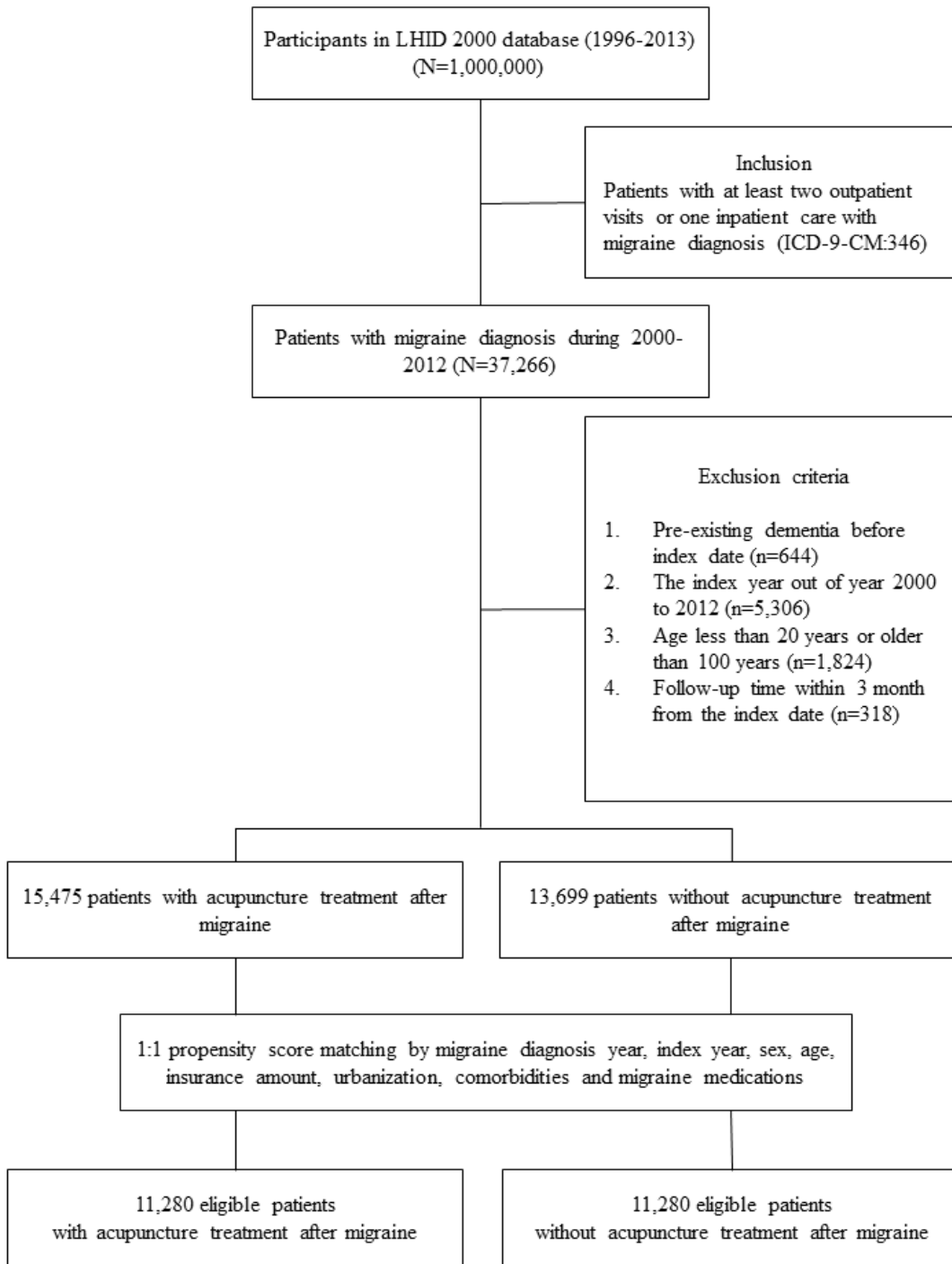


Figure 1

Study population flowchart. 37,266 patients with migraine, newly diagnosed between 2000 and 2012, were identified. A 1:1 propensity score was used to match cohorts based on sex, age, baseline comorbidities, and medication usage. The groups of acupuncture users and nonacupuncture users each contained 11,280 patients. LHID 2000: Longitudinal Health Insurance Database 2000, NHI: National Health Insurance

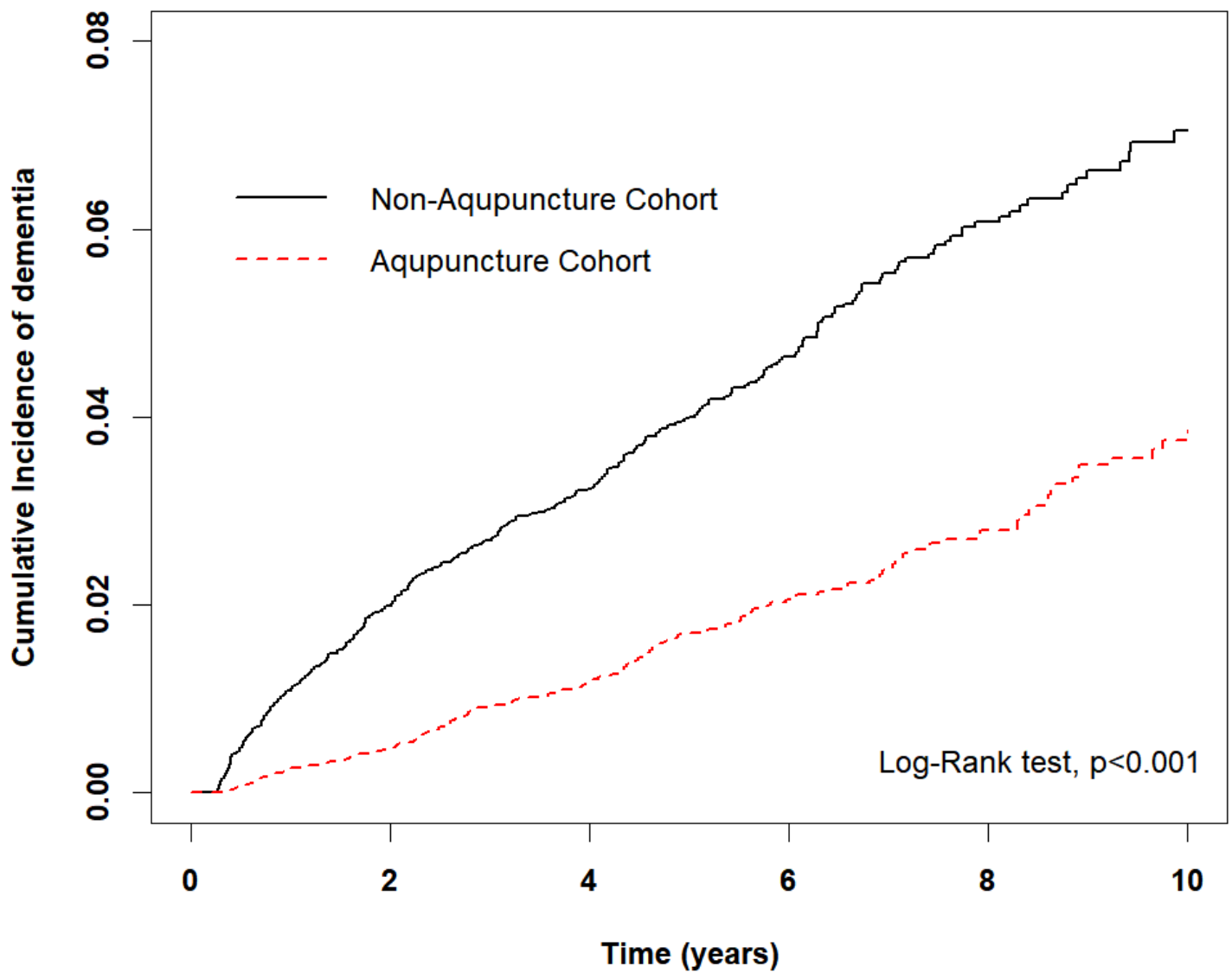


Figure 2

Cumulative incidence of dementia in the acupuncture and nonacupuncture cohorts. Cumulative incidence of dementia in the acupuncture cohort was significantly lower than in the nonacupuncture cohort (log-rank test, $p < 0.0001$).