

# Acupuncture Treatment is Associated with Reduced Dementia Risk in Patients with Migraine: A Propensity-Score–Matched Cohort Study of Real-World Data

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**Background:** Migraine is a recurrent headache disease that has been identified as a risk factor for subsequent dementia. 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 or did not concurrently receive acupuncture treatment.

**Methods:** A 1:1 propensity score method was used to match an equal number of patients (N = 4813) 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.

**Results:** Patients with migraine who received acupuncture treatment were found to have a lower risk of dementia (adjusted hazard ratio [aHR] = 0.51, 95% CI = 0.40–0.65) than those who did not undergo acupuncture treatment. The cumulative incidence of dementia was significantly lower in the acupuncture cohort than in the nonacupuncture cohort (Log rank test,  $p < 0.001$ ). This propensity score–matched cohort study demonstrated an association between acupuncture treatment and dementia development in patients with migraine in Taiwan.

**Conclusion:** The results suggest that acupuncture treatment significantly reduced the development of dementia in patients with migraine.

**Keywords:** acupuncture, migraine, dementia, National Health Insurance Research Database, NHIRD, propensity score, cohort

## Introduction

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.<sup>1</sup> Common symptoms include headache and accompanying nausea, vomiting, photophobia, and occasional sensitivity to taste and sound.<sup>1</sup> 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.<sup>2</sup> 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).<sup>3</sup>

Several studies have indicated that migraine is associated with increased risks of stroke,<sup>4</sup> depression,<sup>5</sup> and dementia.<sup>6</sup> In addition, a cross-sectional prevalence study found that patients with migraine with or without aura are at increased risk

for subclinical brain lesions.<sup>7</sup> Previous studies have revealed that silent brain lesions in the general population double the risk of dementia.<sup>8</sup>

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.<sup>9</sup> 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.<sup>10</sup> Several studies have reported that acupuncture or CHPs are often used to treat migraine.<sup>11,12</sup> A population-based cohort study indicated a decreased risk of dementia in patients with migraine who used CHPs.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup> Another study found migraine to be associated with vascular risk factors and reduced cerebral blood flow (CBF) to be a potential cause of dementia.<sup>16</sup> One clinical trial indicated that CBF was enhanced through acupuncture.<sup>17</sup> In addition, decreased hippocampal volume of newly diagnosed migrainers was discovered,<sup>18</sup> and the hippocampal structural and functional changes play a critical role in the pathophysiology of migraine.<sup>19</sup> A study found that acupuncture treatment can increase the hippocampal connectivity among patients with Alzheimer Disease (AD).<sup>20</sup> 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 9626 patients with migraine between 2000 and 2012 who were identified in the NHIRD.

## Materials and 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)]. All methods were performed in accordance with the relevant guidelines and regulations. 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.

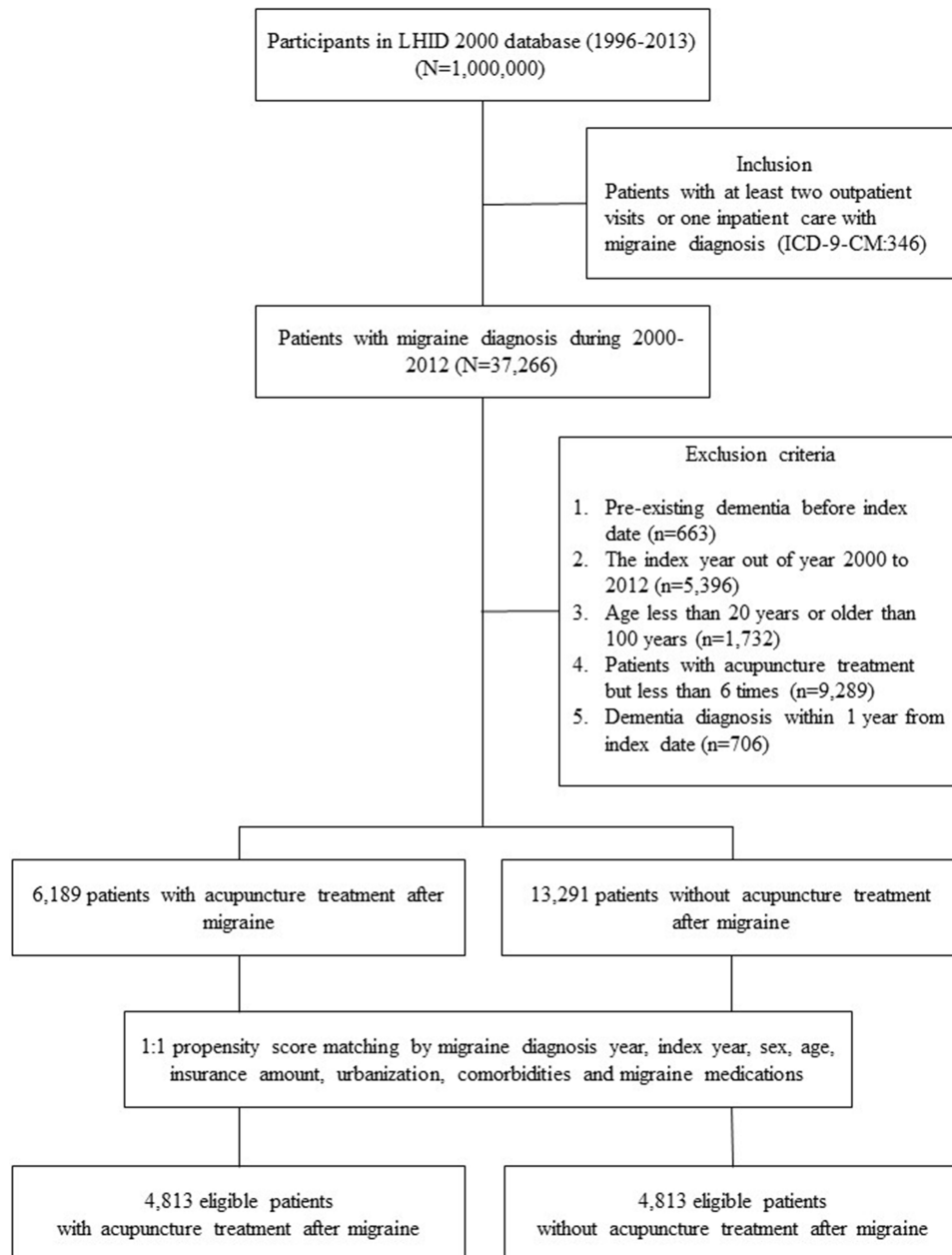
### Study Population

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 after at least one year), withdrew from the NHIRD, or December 31, 2013. The patients with dementia were grouped into those with Alzheimer's disease (AD) (*ICD-9-CM*: 331.0), vascular dementia (VaD) (*ICD-9-CM*: 290.4), or other degenerative dementia (*ICD-9-CM*: 290.x except 290.4).

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. We defined acupuncture cohort based on more than 6 times acupuncture treatments received after diagnosing as migraine during the study period. The matching variables included age, sex, insurance amount, urbanization level, baseline comorbidities, and medication usage (Figure 1).



**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 4813 patients.

**Abbreviations:** LHID 2000, Longitudinal Health Insurance Database 2000; NHI, National Health Insurance.

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 1000 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 4813 patients with migraine who received acupuncture treatment, 75% 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* = 0.0659) and exhibited a higher rate of medication usage for migraine (*p* = 0.2646).

Table 2 displays the diagnosis distribution for patients who received acupuncture treatment. Most received treatment because of injury or poisoning (83.5%) or receiving a diagnosis of a disease of the musculoskeletal system or connective tissue (83.5%).

Several stratified analyses were conducted to verify the associations (Table 3). Patients who received acupuncture treatment exhibited a decreased risk of overall dementia and acupuncture is more effective for other degenerative dementia; this was true for women (aHR = 0.47, 95% CI = 0.35–0.63); men (aHR = 0.56, 95% CI = 0.37–0.85); patients aged 40 to 65 years (aHR = 0.46, 95% CI = 0.30–0.71); patients aged over 65 years (aHR = 0.45, 95% CI = 0.33–0.59); patients with diabetes (aHR = 0.49, 95% CI = 0.33–0.72), hypertension (aHR = 0.55, 95% CI = 0.42–0.72), hyperlipidemia (aHR = 0.54, 95% CI = 0.40–0.75), coronary artery disease (aHR = 0.55, 95% CI = 0.40–0.75), depression (aHR = 0.43, 95% CI = 0.26–0.71), stroke (aHR = 0.63, 95% CI = 0.44–0.90), or chronic kidney disease (aHR = 0.65, 95% CI = 0.42–0.99); and patients without migraine-related medication usage (aHR = 0.59, 95% CI = 0.39–0.87).

Among patients with migraine, the risk of dementia exhibited a dose-dependent decrease with increasing use of acupuncture treatment (Table 4). 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 49% 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.

**Table 1** Characteristics of Newly Diagnosed Patients with Migraine Who Did or Did Not Receive Acupuncture

Variable	Received Acupuncture		p value*
	No (n =4813)	Yes (n =4813)	
	n (%) / Mean (SD)	n (%) / Mean (SD)	
<b>Sex</b>			0.5412
Women	3591 (74.6)	3617 (75.2)	
Men	1222 (25.4)	1196 (24.8)	
<b>Age at baseline</b>			0.4093
Mean±SD (years) <sup>†</sup>	46.6 (15.9)	46.3 (14.4)	
20–39	1826 (37.9)	1685 (35)	
40–65	2273 (47.2)	2530 (52.6)	
>65	714 (14.8)	598 (12.4)	
<b>Insurance amount (NT\$)</b>			0.3454
0–15,840	2118 (44)	2081 (43.2)	
15,841–28,800	1988 (41.3)	1984 (41.2)	
28,801–45,800	513 (10.7)	566 (11.8)	
>45,800	194 (4)	182 (3.8)	
<b>Urbanization<sup>‡</sup></b>			0.0659
1 (highest)	1454 (30.2)	1490 (31)	
2	1536 (31.9)	1431 (29.7)	
3	727 (15.1)	795 (16.5)	
4 (lowest)	1096 (22.8)	1097 (22.8)	
<b>Baseline Comorbidity</b>			
Diabetes mellitus	764 (15.9)	755 (15.7)	0.8013
Hypertension	1416 (29.4)	1388 (28.8)	0.5299
Hyperlipidemia	1587 (33)	1516 (31.5)	0.1215
Coronary artery disease	1015 (21.1)	993 (20.6)	0.5810
Head injury	521 (10.8)	503 (10.5)	0.5518
Depression	817 (17)	797 (16.6)	0.5853
Stroke	619 (12.9)	617 (12.8)	0.9514
Chronic kidney disease	610 (12.7)	600 (12.5)	0.7585
<b>Medications<sup>b</sup></b>			0.2646
0	2634 (54.7)	2647 (55)	
1	1486 (30.9)	1518 (31.5)	
2	528 (11)	515 (10.7)	
≥3	165 (3.4)	133 (2.8)	
<b>Types of acupuncture, n (%)</b>			
Manual acupuncture of TCM type	–	3742 (77.8)	
Electroacupuncture	–	54 (1.1)	
Combination of manual acupuncture and electroacupuncture	–	1017 (21.1)	
<b>Acupuncture visits, times</b>		19.9 (26.7)	

**Notes:** \*Chi-square test; <sup>†</sup>t test; <sup>‡</sup>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; <sup>b</sup>Medications included: Sumatriptan, Rizatriptan, Ergotamine, Naproxen, Diclofenac, Caffeine, Acetaminophen, Etoricoxib, Celecoxib, ibuprofen.

Previous studies have reported that acupuncture can exert preventive effects in populations with several diseases associated with dementia, including traumatic brain injury (TBI),<sup>21</sup> stroke,<sup>22</sup> and hypertension.<sup>23</sup> 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 or aged over 65 years had a higher risk of dementia than younger individuals. The risk of developing dementia after age 60 was higher among

**Table 2** Distribution of Acupuncture Cohort by Disease Category or Diagnosis in Patients with Migraine

Disease (ICD-9-CM)	Acupuncture Users (n=4813)
	n (%)
Infectious and parasitic disease (001–139)	21 (0.4)
Neoplasms (140–239)	30 (0.6)
Malignant (140–208)	20 (0.4)
Benign (210–229)	12 (0.2)
Endocrine, nutritional and metabolic disease and immunity disorder (240–279)	54 (1.1)
Blood and blood-forming organs (280–289)	19 (0.4)
Mental disorder (290–319)	101 (2.1)
Nervous system (320–389)	722 (15)
Circulatory system (390–459)	171 (3.6)
Respiratory system (460–519)	435 (9.0)
Digestive system (520–579)	492 (10.2)
Genitourinary system (580–629)	225 (4.7)
Complications of pregnancy, childbirth and the puerperium (630–676)	3 (0.1)
Skin and subcutaneous tissue (680–709)	73 (1.5)
Musculoskeletal system and connective tissue (710–739)	4018 (83.5)
Congenital anomalies (740–759)	38 (0.8)
Certain conditions originating in the perinatal period (760–779)	1 (0.0)
Symptoms, signs and ill-defined conditions (780–799)	1131 (23.5)
Injury and poisoning (800–999)	4021 (83.5)

individuals with migraine in midlife than among individuals without.<sup>24</sup> Therefore, aging can be identified as a key factor that increases the incidence of dementia.<sup>25</sup>

Of all the baseline comorbidities associated with migraine, including hypertension, depression, coronary artery disease, 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.<sup>26</sup> Early life depressive symptoms have been revealed to be related to a 2-fold or greater increase in the risk of dementia.<sup>27</sup> Heart disease and cardiovascular risk factors in midlife are confirmed to the development of dementia in later life.<sup>28</sup> In addition, studies on stroke have revealed that vascular risk factors may also be independent risk factors for developing dementia.<sup>29</sup> In this study, acupuncture was found to potentially reduce the incidence of dementia in migraine patients with these comorbidities.

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 (83.5%) and those affected by injury or poisoning (83.5%). Injury and disorders of the musculoskeletal system or connective tissue were the predominant reasons for patients to seek acupuncture treatment.<sup>15</sup> A previous study indicated that patients with migraine exhibited significantly more musculoskeletal dysfunction than migraine-free control participants, especially muscle tension in the neck.<sup>30</sup> Most patients had cervical musculoskeletal impairments that accompanied their migraine episodes.<sup>31,32</sup> In addition, a case report suggested chronic carbon monoxide (CO) intoxication may mimic migraine attacks.<sup>33</sup> Therefore, acupuncture is a safe form of intervention and is a feasible option for patients with chronic neck pain or carbon monoxide intoxication.<sup>34,35</sup>

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).<sup>36</sup> A population-based database study indicated that TBI is a risk factor for migraine.<sup>37</sup> Combining acupuncture with a TBI treatment regimen was reported to reduce the risk of dementia by 35%.<sup>21</sup> Therefore, acupuncture can not only reduce TBI symptoms but also prevent subsequent dementia.



**Table 3** Incidence Rates, Hazard Ratios, and Confidence Intervals of Dementia for Patients with Migraine Who Did and Did Not Receive Acupuncture in Different Stratifications

Variables	Received Acupuncture						Compared with Non-Acupuncture Users	
	No (n=4813)			Yes (n=4813)			Crude HR	Adjusted HR <sup>†</sup>
	Event	Person Years	IR	Event	Person Years	IR	(95% CI)	(95% CI)
<b>Overall</b>	215	29,729	7.23	99	32,268	3.07	0.42 (0.33–0.53)***	0.51 (0.40–0.65)***
<b>Alzheimer's disease</b>	11	29,729	0.37	7	32,268	0.22	0.57 (0.22–1.47)	0.70 (0.27–1.83)
<b>Vascular dementia</b>	11	29,729	0.37	8	32,268	0.25	0.66 (0.26–1.64)	0.94 (0.36–2.41)
<b>Other degenerative dementia</b>	193	29,729	6.49	84	32,268	2.60	0.40 (0.31–0.51)***	0.47 (0.37–0.62)***
<b>Sex</b>								
Women	147	21,976	6.69	64	24,032	2.66	0.40 (0.29–0.53)***	0.47 (0.35–0.63)***
Men	68	7752	8.77	35	8236	4.25	0.48 (0.32–0.72)**	0.56 (0.37–0.85)**
<b>Age group</b>								
20–39	2	11,867	0.17	0	11,816	0.00	-	-
40–65	57	14,196	4.02	33	16,951	1.95	0.48 (0.31–0.73)**	0.46 (0.30–0.71)**
>65	156	3666	42.55	66	3501	18.85	0.43 (0.33–0.58)***	0.45 (0.33–0.59)***
<b>Insurance amount (NT\$)</b>								
0–15,840	80	12,704	6.30	43	13,517	3.18	0.50 (0.35–0.73)**	0.54 (0.37–0.79)**
15,841–28,800	118	12,491	9.45	45	13,818	3.26	0.34 (0.24–0.48)***	0.46 (0.33–0.66)***
28,801–45,800	15	3336	4.50	8	3737	2.14	0.49 (0.21–1.14)	0.30 (0.12–0.78)*
>45,800	2	1198	1.67	3	1196	2.51	1.47 (0.25–8.78)	0.25 (0.01–8.51)
<b>Urbanization</b>								
1 (highest)	57	8645	6.59	29	9540	3.04	0.46 (0.29–0.71)**	0.42 (0.27–0.66)**
2	65	9546	6.81	26	9520	2.73	0.40 (0.25–0.63)***	0.46 (0.29–0.73)**
3	22	4617	4.77	16	5313	3.01	0.65 (0.34–1.24)	0.77 (0.39–1.50)
4 (lowest)	71	6921	10.26	28	7896	3.55	0.34 (0.22–0.53)***	0.50 (0.32–0.78)**
<b>Baseline Comorbidity (ref=nonsite comorbidity)</b>								
Diabetes mellitus	82	4319	18.99	41	4797	8.55	0.45 (0.31–0.65)***	0.49 (0.33–0.72)**
Hypertension	171	9138	18.71	81	9645	8.40	0.44 (0.34–0.58)***	0.55 (0.42–0.72)***
Hyperlipidemia	121	7988	15.15	58	8549	6.78	0.44 (0.32–0.60)***	0.54 (0.40–0.75)**
Coronary artery disease	129	5825	22.15	62	6347	9.77	0.44 (0.32–0.59)***	0.55 (0.40–0.75)**
Head injury	24	3005	7.99	11	2995	3.67	0.45 (0.22–0.92)*	0.90 (0.42–1.94)
Depression	54	4586	11.77	21	4907	4.28	0.36 (0.22–0.60)***	0.43 (0.26–0.71)**
Stroke	90	3414	26.36	49	3814	12.85	0.48 (0.34–0.68)***	0.63 (0.44–0.90)*
Chronic kidney disease	66	3365	19.61	34	3838	8.86	0.44 (0.29–0.67)**	0.65 (0.42–0.99)*
<b>Medications</b>								
0	80	14,164	5.65	37	15,970	2.32	0.40 (0.27–0.60)***	0.59 (0.39–0.87)**
1	77	10,159	7.58	38	11,056	3.44	0.45 (0.31–0.67)***	0.49 (0.33–0.72)**
2	40	4074	9.82	18	4085	4.41	0.45 (0.26–0.78)**	0.48 (0.27–0.86)*
≥3	18	1332	13.51	6	1157	5.19	0.39 (0.16–0.98)*	0.35 (0.14–0.93)*

**Notes:** Adjusted <sup>†</sup>HR 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.

**Abbreviations:** IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.

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.<sup>38–41</sup> 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.<sup>42</sup> Olesen et al,<sup>43</sup> after observing changes in CBF, proposed that the mechanism of migraine-induced cerebral

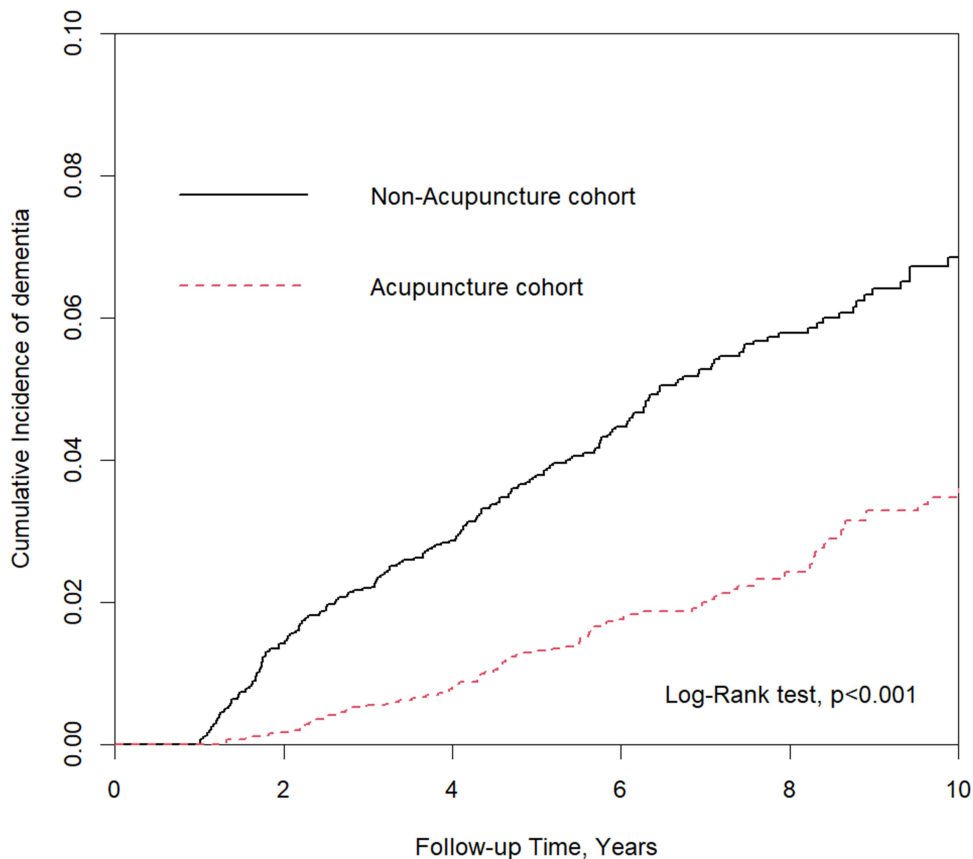
**Table 4** Risk of Dementia and Number of Acupuncture in Migraine Patients

Number of Acupuncture	N	Event	Crude HR	p-value	Adjusted HR <sup>†</sup>	p-value
0	4813	215	ref.		ref.	
6–11	2339	41	0.40 (0.28–0.55)	<0.0001	0.55 (0.40–0.78)	0.0006
12–17	957	23	0.49 (0.32–0.76)	0.0013	0.66 (0.43–1.02)	0.0633
18–23	464	8	0.33 (0.16–0.67)	0.0021	0.35 (0.17–0.72)	0.0039
≥24	1053	27	0.44 (0.30–0.66)	<0.0001	0.42 (0.28–0.63)	<0.0001

**Notes:** Adjusted <sup>†</sup>HR 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.

ischemia is spreading cortical depression. The fall in CBF can also rapidly increase the deposition of amyloid  $\beta$  ( $A\beta$ ) and drive cognitive decline that occurs early in the development of AD patients.<sup>44</sup> However, this proposition related only to migraines with aura. Another study found that the vascular factors of migraine may be related to the risk of dementia because changes in the brain indicated that cerebral small vessel disease increases the risk of most dementia types and cerebrovascular dysfunction.<sup>24</sup> Yet another study determined that acupuncture at the Baihui (GV20) and Yintang (GV29) points increased the CBF of the prefrontal lobe and hippocampus in mouse models of Alzheimer's disease.<sup>45</sup> Moreover, a pilot study demonstrated a significant increase in CBF after true acupuncture in patients with stroke.<sup>17</sup> 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 and are associated with migraine.<sup>40,46</sup> High-resolution evidence has indicated that WHMs give rise to cognitive impairment and play a crucial role in the



**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,  $p < 0.001$ ).



development of dementia.<sup>8,40</sup> Acupuncture at the Baihui (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.<sup>47</sup> 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.<sup>48</sup> 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.<sup>39,49</sup> 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 $\beta$ , IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), or interferon- $\gamma$  (INF- $\gamma$ ).<sup>39</sup> Oxidative stress, which induces excessive production of free radical species, could lead to oxidative biomolecules and expedite aging.<sup>50</sup> Electroacupuncture (EA) was found to decrease the serum levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in a rat model of migraine.<sup>51</sup> 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.<sup>52</sup> 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.<sup>38</sup> Several mechanisms may link depression and dementia, including 1) vascular disease, 2) increased deposition of  $\beta$ -amyloid, 3) inflammatory changes, and 4) small hippocampal volumes.<sup>27,53</sup> Acupuncture has been identified as having potential to enhance CBF in both animals and humans.<sup>17,45</sup> 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.<sup>54</sup> Acupuncture also significantly decreased the serum levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in a chronic stress model of depression in rats.<sup>55</sup> In addition, a fMRI study revealed that acupuncture treatment strengthen the hippocampal connectivity in AD patients.<sup>20</sup> A previous rat study found that acupuncture improved cognition and hippocampal synaptic plasticity through activation of D1/D5 receptors.<sup>56</sup> Acupuncture, through multiple depression-associated pathways, could therefore reduce the risk of dementia in patients with migraine by increasing CBF, decreasing A $\beta$  generation, decreasing the contents of proinflammatory cytokines, and increasing neuron density of the hippocampus in the brain.

The present study leaves open one key question: the mean number of acupuncture visits was 19.9 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.<sup>57</sup> Acupuncture not only decreases migraine recurrence for an extended period but also reduces the need for rescue medication.<sup>58</sup> 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.<sup>59</sup> 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.

## Limitations

The present study had other limitations that should be addressed. First, the data file from LHID 2000 we used was provided by Taiwan National Health Research Institutes (NHRI), which had been authorized by the Ministry of Health and Welfare to manage the claims data of the national health insurance. The latest update database by NHRI is not available now. Second, 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. Third, 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. Fourth, 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. Fifth, because some cases of dementia are late onset, the duration of the current study's follow-up period was insufficient to capture these.

## Conclusions

Patients with migraine may receive complementary therapies in Taiwan, and most of them would like to choose acupuncture treatment. 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 is associated with a reduced risk of dementia. Our study emphasizes the need for additional clinical trials that include laboratory data and brain imaging to identify potential preventive mechanisms.

## Data Sharing Statement

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>).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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