

BMJ Open Risk of dementia in patients with non-haemorrhagic stroke receiving acupuncture treatment: a nationwide matched cohort study from Taiwan's National Health Insurance Research Database

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ABSTRACT

Objective To investigate the risk of dementia in patients with stroke who did and did not receive acupuncture treatment.

Design Retrospective cohort study.

Setting This study was based on Taiwan's National Health Insurance Research Database that included patients with stroke hospitalised between 1 January 2000 and 31 December 2004.

Participants We identified 11 220 patients aged 50 years and older with newly diagnosed stroke hospitalisation.

Primary and secondary outcome measures We compared the incident dementia during the follow-up period until the end of 2009 in patients with stroke who did and did not receive acupuncture. The adjusted HRs and 95% CIs of dementia associated with acupuncture were calculated in multivariate Cox proportional hazard regressions.

Results Acupuncture treatment was associated with a decreased risk of dementia with multivariate adjustment (HR, 0.73; 95% CI 0.66 to 0.80), and the association was significant in both sexes and every age group, as well as in groups with ischaemic stroke, with fewer medical conditions and those hospitalised after stroke. Patients with stroke received acupuncture treatment, and conventional rehabilitation was associated with a significantly reduced risk of poststroke dementia (HR, 0.64; 95% CI 0.56 to 0.74).

Conclusions This study raises the possibility that patients with non-haemorrhagic stroke who received acupuncture had a reduced risk of dementia. The results suggest the need for prospective sham-controlled and randomised trials to establish the efficacy of acupuncture in preventing dementia.

INTRODUCTION

Dementia represents a major burden of disease worldwide. An estimated 47 million people lived with dementia in 2015, and the ageing of the population worldwide is expected to triple this number by 2050.¹ Dementia also represents a substantial

Strengths and limitations of this study

- We used a matching procedure with a propensity score to reduce the confounding effects.
- Multivariate Cox proportional hazard models were used to control the residual confounding bias.
- Our data lacked clinical risk scores, lesion characteristics, biochemical measures and lifestyles of patients with stroke.
- The actual acupuncture points used in the treatment were not available.
- The mode of acupuncture treatment for patients with stroke varied among traditional Chinese medicine physicians.

financial burden on society; for example, US dementia care costs are estimated to reach \$215 billion per year.² Dementia commonly occurs after a stroke, with the 1-year incidence of poststroke dementia ranging from 7.4% to 41.3%.³ Poststroke dementia is one of the major determinants of dependency among patients with stroke, and it also predicts the recurrence of ischaemic stroke in long-term follow-up.^{4,5}

Given ageing populations and declining mortality after a stroke,⁵ it is important to prevent dementia among stroke survivors. Strategies have been suggested to reduce cognitive decline and the subsequent risk of dementia; these include regular physical activity, increased fruit and vegetable consumption, and the management of medical risk factors (diabetes, obesity, smoking, depression and hypertension).^{6,7} Nevertheless, active interventions to prevent poststroke dementia deserve further investigation.⁸

Acupuncture is a technique in which fine needles are inserted and manipulated at specific points on the body to achieve therapeutic purposes, and it is integral to everyday medical practice in many nations around the world.⁹ A 2002–2007 US study found some 3.1 million adults and 150 000 children had acupuncture in the previous year, as reported in the 2007 National Health Interview Survey.^{9 10} While some clinical studies and systematic reviews support acupuncture's effectiveness in poststroke rehabilitation,^{11–15} these therapeutic effects remain unclear due to poor methodology and small sample sizes.

Whether acupuncture is effective in reducing dementia in patients with stroke remains unknown. Using the Taiwan National Health Insurance Research Database, we conducted a nationwide matched cohort study to investigate the results of acupuncture treatment in reducing poststroke dementia.

PATIENTS AND METHODS

Source of data

Research data were obtained from the reimbursement claims of Taiwan's National Health Insurance Programme, which was implemented in March 1995 and covers more than 99% of Taiwan's 23 million residents. The National Health Research Institutes established a National Health Insurance Research Database, which records all beneficiaries' medical services for public research interest. This information includes inpatient and outpatient demographics, primary and secondary diagnoses, procedures, prescriptions, and medical expenditures. The validity of this database has been favourably evaluated, and research articles based on it have been accepted in prominent scientific journals worldwide.^{8 16–18}

Ethical approval

Insurance reimbursement claims used in this study were from Taiwan's National Health Insurance Research Database, which is available for research access. This study was conducted in accordance with the Helsinki Declaration. To protect personal privacy, the electronic database was decoded with patient identification scrambled for further academic access for research. According to the National Health Research Institutes regulations, informed consent is not required because of the use of decoded and scrambled patient identification. This study was evaluated and approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB-201505055) and E-DA Hospital (EDA-JIRB-2014012).

Study design

Of the 23 million people in Taiwan, we identified 226 699 new stroke survivors aged ≥ 50 years admitted to the hospital (people who visited inpatient care with a physician's primary diagnosis of stroke) between 1 January 2000 and 31 December 2004. The diagnosis of stroke was validated in previous studies.^{8 16–18} To confirm that all patients with stroke in our study were incident cases,

only new-onset stroke cases were included; patients with previous records of stroke within 5 years before the index date were excluded. Among the subjects, 5610 received at least five courses (one course consisted of six consecutive treatments) of acupuncture treatment after stroke admission. To select appropriate study subjects, patients with stroke with only one to four courses of acupuncture treatment were excluded. Patients with stroke without acupuncture treatment were selected by a matched pair procedure with propensity score (exposure vs non-exposure ratio=1:1). For the non-acupuncture group, patients with stroke were followed up from the discharge date following stroke admission (index date) until 31 December 2009, or until the dementia event occurred, was lost to follow-up or death. For the acupuncture group, patients with stroke were followed up from the first date of receiving acupuncture treatment after stroke admission (index date) until 31 December 2009, or until the dementia event occurred, was lost to follow-up or death. In the acupuncture group, the time period between discharge date after stroke admission and the date of first acupuncture treatment after stroke admission was the immortal time. Therefore, the immortal time bias (resulting from the overestimation of the intervention's beneficial effects) was avoided in this study. The follow-up time, in person-years, was calculated for each patient with stroke from the index date to the end point. We compared the risk of incident dementia between patients with stroke who did and did not receive acupuncture treatment during the follow-up period.

Criteria and definition

In this study, low-income patients were defined as those qualifying for waived medical copayment, because this status is verified by the National Health Insurance system. We calculated the population density (persons/km²) for each of all administrative units in Taiwan. Based on population density, these units were stratified into tertiles to designate areas of low, moderate and high urbanisation. We defined newly diagnosed stroke according to the *International Classification of Diseases, 9th Revision, Clinical Modification*, as ICD-9-CM 430–437. The primary outcome as the incident event of dementia was defined by patients who sought medical care with a physician's primary diagnosis of dementia (ICD-9-CM 290). Coexisting medical conditions were determined from medical claims for the follow-up period and included hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), mental disorders (ICD-9-CM 290–319), chronic obstructive pulmonary disease (ICD-9-CM 490–496), ischaemic heart disease (ICD-9-CM 410–414), urinary tract infection (ICD-9-CM 599.0), hyperlipidaemia (ICD-9-CM 272.0–272.4), pneumonia (ICD-9-CM 480–486), congestive heart failure (ICD-9-CM 428), epilepsy (ICD-9-CM 345) and liver cirrhosis (ICD-9-CM 571). Renal dialysis was defined by the administration code (D8, D9). Subtypes of stroke, staying in a medical centre or not, length of hospital stay, admission to the intensive care unit, or receiving neurosurgery

during the index stroke hospitalisation were also identified as potential confounding factors. Medications for stroke (anticoagulants, antiplatelet agents and lipid-lowering agents) were also considered.

Statistical analysis

To reduce confounding effects, we developed a non-parametric multivariable logistic regression model to estimate a propensity score for acupuncture treatment. Clinical significance guided the initial choice of covariates. These included age, sex, low-income status, urbanisation, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, ischaemic heart disease, urinary tract infection, hyperlipidaemia, pneumonia, congestive heart failure, epilepsy, liver cirrhosis, renal dialysis, subtypes of stroke, stay in a medical centre, length of hospital stay, admission to the intensive care unit and receiving neurosurgery. We used a structured iterative approach to refine this logistic regression model to achieve a balance of covariates within matched pairs. We then matched (without replacement) patients who had acupuncture treatment with those who did not using a greedy matching algorithm with a calliper width of 0.2 SD of the propensity score log odds. The nearest neighbour algorithm was applied to construct matched pairs, assuming that the proportion of 0.95–1.0 was perfect. This method could remove 98% of the bias from measured covariates.^{19 20}

To compare the balance between groups after the application of the propensity score, χ^2 tests were used to analyse categorised data between patients with stroke who did and did not receive acupuncture treatment. The mean and SD for age and length of hospital stay for patients with stroke with and without acupuncture treatment were compared using t-tests. We used a multivariable Cox proportional hazard model to analyse the adjusted HRs and 95% CIs for incident dementia associated with acupuncture treatment in patients with stroke. All analyses were performed using Statistical Analysis Software V.9.1. A two-sided p value of <0.05 was considered to be significant.

RESULTS

After propensity score matching (table 1), there were no significant differences in the distributions of age, sex, low-income status, urbanisation, stay in a medical centre, length of hospital stay, stay in the intensive care unit, type of stroke, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, ischaemic heart disease, urinary tract infection, hyperlipidaemia, pneumonia, congestive heart failure, epilepsy, renal dialysis, liver cirrhosis, physical rehabilitation, anticoagulants, antiplatelet agents and lipid-lowering agents between patients with stroke who did and did not receive acupuncture treatment.

During the follow-up period (table 2), patients with stroke with acupuncture treatment had a lower incidence of newly diagnosed dementia (26.5 per 1000 person-years)

Table 1 The characteristics of stroke patients with and without acupuncture treatment

	Acupuncture treatment		p Value
	No (n=5610)	Yes (n=5610)	
Sex	n (%)	n (%)	1.00
Female	2424 (43.2)	2424 (43.2)	
Male	3186 (56.8)	3186 (56.8)	
Age at first stroke			1.00
50–59	1368 (24.4)	1368 (24.4)	
60–69	2242 (40.0)	2242 (40.0)	
70–79	1770 (31.5)	1770 (31.5)	
≥80	230 (4.1)	230 (4.1)	
Low income	21 (0.4)	21 (0.4)	1.00
Urbanisation			1.00
Low	76 (1.3)	76 (1.3)	
Moderate	1794 (32.0)	1794 (32.0)	
High	3740 (66.7)	3740 (66.7)	
Stay in medical centre	3616 (64.5)	3616 (64.5)	1.00
Length of stay, mean±SD	6.70±4.92	6.74±5.01	0.66
Stay in intensive care unit	355 (6.3)	355 (6.3)	1.00
Neurosurgery	86 (1.5)	86 (1.5)	1.00
Types of stroke			1.00
Haemorrhage	464 (8.3)	464 (8.3)	
Ischaemic	3386 (60.3)	3386 (60.3)	
Others	1760 (31.4)	1760 (31.4)	
Coexisting medical condition			1.00
Hypertension	4254 (75.8)	4254 (75.8)	1.00
Diabetes	1923 (34.3)	1923 (34.3)	1.00
Mental disorder	1837 (32.8)	1837 (32.8)	1.00
Chronic obstructive pulmonary disease	1640 (29.2)	1640 (29.2)	1.00
Ischaemic heart disease	1333 (23.8)	1333 (23.8)	1.00
Urinary tract infection	950 (16.9)	950 (16.9)	1.00
Hyperlipidaemia	592 (10.6)	592 (10.6)	1.00
Pneumonia	545 (9.7)	545 (9.7)	1.00
Congestive heart failure	129 (2.3)	129 (2.3)	1.00
Epilepsy	26 (0.5)	26 (0.5)	1.00
Renal dialysis	15 (0.3)	15 (0.3)	1.00
Liver cirrhosis	9 (0.2)	9 (0.2)	1.00
Rehabilitation	3794 (67.6)	3794 (67.6)	1.00
Anticoagulants	44 (0.8)	44 (0.8)	1.00

Continued

Table 1 Continued

	Acupuncture treatment		p Value
	No (n=5610)	Yes (n=5610)	
Antiplatelet agents	2628 (46.8)	2628 (46.8)	1.00
Lipid-lowering agents	594 (10.6)	594 (10.6)	1.00

than those without acupuncture treatment (34.6 per 1000 person-years), with an HR of 0.73 (95% CI 0.66 to 0.80)

after adjustment for age, sex, low-income status, urbanisation, stay in a medical centre, length of hospital stay, stay in the intensive care unit, types of stroke, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, ischaemic heart disease, urinary tract infection, hyperlipidaemia, pneumonia, congestive heart failure, epilepsy, renal dialysis, liver cirrhosis, physical rehabilitation, anticoagulant, antiplatelet agents and lipid-lowering agents. The log-rank test (figure 1) indicated that patients with stroke with acupuncture treatment had a lower probability of newly diagnosed dementia events than those without acupuncture treatment ($p < 0.0001$).

Among patients with stroke (table 3), the decreased risk of newly diagnosed dementia associated with acupuncture treatment was significant in men (HR, 0.75; 95% CI 0.66 to 0.85) and women (HR, 0.70; 95% CI 0.60 to 0.80). The age-stratified results revealed adjusted HRs for dementia associated with acupuncture treatment for patients with stroke aged 50–59 years (HR, 0.64; 95% CI 0.47 to 0.86), 60–69 years (HR, 0.75; 95% CI 0.64 to 0.88), 70–79 years (HR, 0.72; 95% CI 0.63 to 0.83) and ≥ 80 years (HR, 0.54; 95% CI 0.38 to 0.76). The associations between reduced dementia and acupuncture treatment were also significant in patients with ischaemic stroke (HR, 0.74; 95% CI 0.66 to 0.84), other stroke (HR, 0.69; 95% CI 0.57 to 0.82), no medical conditions (HR, 0.55; 95% CI 0.39 to 0.77), 1 medical condition (HR, 0.64; 95% CI 0.52 to 0.80), 2 medical conditions (HR, 0.81; 95% CI 0.68 to 0.98), ≥ 3 medical conditions (HR, 0.82; 95% CI 0.71 to 0.95), < 7 days of hospital stay (HR, 0.81; 95% CI 0.71 to 0.91) and ≥ 7 days of hospital stay (HR, 0.64; 95% CI 0.55 to 0.74).

Table 4 shows the joint effects of acupuncture and rehabilitation on dementia risk. Compared with patients with stroke who did not receive acupuncture and rehabilitation, patients with stroke receiving acupuncture and rehabilitation had the lowest risk of dementia (HR, 0.64; 95% CI 0.56 to 0.74). The beneficial effects for reducing dementia risk were also shown in patients with stroke who received acupuncture treatment but not rehabilitation (HR, 0.76; 95% CI 0.64 to 0.90).

DISCUSSION

This study found that patients with stroke receiving acupuncture treatment exhibited a significantly lower

Table 2 Incidence and adjusted risks of dementia during the follow-up period in patients with stroke with and without acupuncture treatment

	N	Person-years	Events	Incidence* HR	Model 1		Model 2		Model 3		Model 4		Model 5	
					(95% CI)	HR	(95% CI)							
No acupuncture	5610	29 594	1025	34.6	1.00	(reference)								
Acupuncture	5610	27 208	720	26.5	0.76	(0.69 to 0.83)	0.76	(0.69 to 0.84)	0.76	(0.69 to 0.84)	0.75	(0.68 to 0.83)	0.73	(0.66 to 0.80)

Model 1: unadjusted.

Model 2: adjusted for age and sex.

Model 3: adjusted for age, sex, urbanisation, low income and stay in medical centre.

Model 4: adjusted for covariates in model 3 plus subtypes of stroke, intensive care unit stay, neurosurgery and length of stay.

Model 5: adjusted for covariates in model 4 plus hypertension, diabetes, mental disorder, chronic obstructive pulmonary disease, ischaemic heart disease, urinary tract infection, hyperlipidaemia, pneumonia, congestive heart failure, epilepsy, renal dialysis and liver cirrhosis.

*Per 1000 person-years.

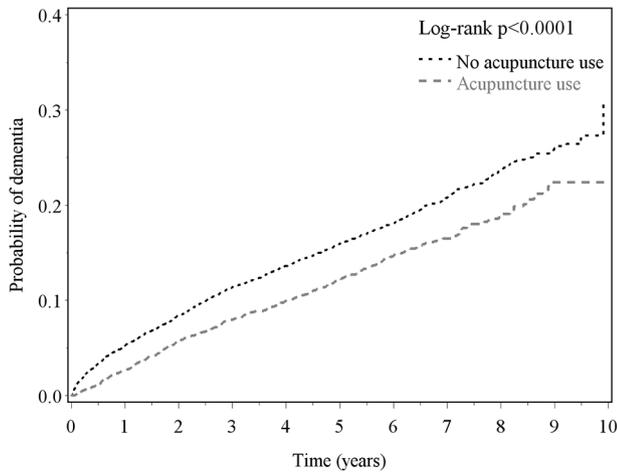


Figure 1 Cumulative incidence of dementia for patients with stroke with and without acupuncture treatment during the follow-up period.

risk of dementia during the follow-up period compared with those without acupuncture in both sexes and people aged more than 50 years, but not in patients with haemorrhagic stroke. To our knowledge, this study may be the first report to show the results of acupuncture treatment on poststroke dementia.

Factors associated with poststroke dementia included age, sex, diabetes, traumatic brain injury and heart disease.^{3 21 22} To reduce confounding effects, we used multiple regressions to adjust sociodemographics (age, sex, low income, urbanisation), characteristics of stroke admission (subtypes of stroke, stay in medical centre, length of hospital stay, admission to intensive care unit, neurosurgery) and medical conditions (hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, ischaemic heart disease, urinary tract infection, hyperlipidaemia, pneumonia, congestive heart failure, epilepsy, liver cirrhosis, renal dialysis). In addition, these potential confounding factors were also matched by propensity score. The strengths of our study include this matching by propensity score and the retrospective cohort study, multivariate regression model, adjustment for immortal time bias and large sample size.

We found that the association between the reduced risk of poststroke dementia and acupuncture treatment existed in patients with stroke of both sexes aged ≥ 50 years, with a greater protective effect in patients with fewer medical conditions and those admitted to the hospital after their stroke. From an epidemiological viewpoint, the above phenomena validated the beneficial effects of acupuncture treatment in reducing risk of poststroke dementia. However, our subgroup analysis found that patients with haemorrhagic stroke who received acupuncture treatment did not show a reduced risk of dementia during the follow-up period. Patients with haemorrhagic stroke had poorer outcomes (such as mortality, dependency, disabilities and modified Rankin Scale score) than those with ischaemic stroke.²³ Patients with haemorrhagic stroke were also more likely to develop dementia

than those experiencing ischaemic and other types of stroke.³ According to the previous studies based on the data from Taiwan's National Health Insurance Research Database,^{24 25} patients with haemorrhagic stroke had a longer length of hospital stay and higher mortality than patients with ischaemic stroke. The greater severity in patients with haemorrhagic stroke may have diluted the effect of acupuncture on reducing poststroke adverse outcomes.^{26 27} Additionally, the small sample size of dementia cases in the patients with haemorrhagic stroke also decreased the statistical significance of acupuncture's effect. These two reasons might explain why there was no significant reduction in the risk of dementia in patients with haemorrhagic stroke who received acupuncture treatment. In addition, our analyses show that combined acupuncture treatment and rehabilitation has the most beneficial effect in reducing dementia risk. This finding is not surprising because one of our previous studies showed reduced dementia in patients with stroke who received conventional rehabilitation.⁸

Acupuncture is one of several treatments used in rehabilitation programmes for patients with stroke and is generally considered safe and well-tolerated.^{12 15} The incidence of acupuncture-related adverse reactions is relatively low, particularly when treating patients with Alzheimer's disease or cerebral infarction.^{9 28–30} In a large cross-sectional study of more than 34000 acupuncture treatments in the UK in 2001, no serious adverse events (such as hospitalisation, permanent disability or death) were reported in relation to acupuncture treatment, and the rate of underlying minor adverse events (such as nausea, fainting, prolonged aggravation of existing symptoms and psychological or emotional reaction) was reported to be 0–1.1 per 10000 treatments.^{9 29} Nevertheless, the surveillance of major or minor adverse events during acupuncture treatment is necessary in future studies.

To clarify the effects of acupuncture treatment in reducing dementia in patients with stroke, we propose some possible explanations. First, acupuncture treatment (acupoints: *Tai chong* (Liv3) and *He gu* (LI4)) can cause activation in the regions with decreased activity; it can also cause deactivation in the regions with increased activity for patients with mild cognitive impairment and Alzheimer's disease.³¹ Second, several studies show acupuncture's effectiveness in improving physical abilities as well as wellness indicators, such as blood pressure.^{12 32} Acupuncture has been found to reduce or relieve depression,^{33 34} anxiety,³⁵ obesity,³⁶ migraine³⁷ and Parkinson's disease^{34 38}; these factors are also associated with increased risk of dementia.^{39–43} Third, patients with stroke who choose acupuncture treatment may have better knowledge, attitudes and practices regarding physical rehabilitation and disease prevention; these factors could also contribute to reduced incidence of dementia after stroke.

This study has some limitations. First, we used insurance claims data that lacked information on clinical risk scores

Table 3 Risks of dementia associated with acupuncture treatment in patients with stroke stratified by age, sex, type of stroke, medical conditions and length of stay*

Stratification	Acupuncture treatment						Yes			
	N	Events	PYs	Incidence† HR	(95% CI)	N	Events	PYs	Incidence* HR	(95% CI)‡
Sex										
Female	2426	467	13 132	35.6	1.00	2426	305	12 015	25.4	0.70 (0.60 to 0.80)
Male	3189	558	16 471	33.9	1.00	3189	415	15 193	27.3	0.75 (0.66 to 0.85)
Age, years										
50–59	1368	116	8137	14.3	1.00	1368	69	7195	9.6	0.64 (0.47 to 0.86)
60–69	2242	355	12 634	28.1	1.00	2242	250	11 235	22.3	0.75 (0.64 to 0.88)
70–79	1770	474	8112	58.4	1.00	1770	348	7989	43.6	0.72 (0.63 to 0.83)
≥80	230	80	712	112.4	1.00	230	53	788	67.3	0.54 (0.38 to 0.76)
Subtypes of stroke										
Haemorrhagic	464	64	2504	25.6	1.00	464	49	2322	21.1	0.77 (0.53 to 1.12)
Ischaemic	3386	664	17 380	38.2	1.00	3386	479	16 214	29.5	0.74 (0.66 to 0.84)
Others	1760	297	9710	30.6	1.00	1760	192	8671	22.1	0.69 (0.57 to 0.82)
Medical conditions										
0	428	84	1480	56.8	1.00	428	60	1821	32.9	0.55 (0.39 to 0.77)
1	1298	210	6263	33.5	1.00	1298	140	6073	23.1	0.64 (0.52 to 0.80)
2	1554	265	8175	32.4	1.00	1554	196	7398	26.5	0.81 (0.68 to 0.98)
≥3	2330	466	13 677	34.1	1.00	2330	324	11 915	27.2	0.82 (0.71 to 0.95)
Length of stay, days										
1–6	3449	609	19 024	32.0	1.00	3405	441	16 712	26.4	0.81 (0.71 to 0.91)
≥7	2161	416	10 570	39.4	1.00	2205	279	10 495	26.6	0.64 (0.55 to 0.74)

*For all patients with haemorrhagic stroke (n=19761) without any matching procedures, acupuncture was associated with reduced risk of dementia (adjusted HR 0.69, 95% CI 0.61 to 0.79).

†Per 1000 PYs.

‡Adjusted for all covariates listed in table 1.

PY, person-years.

Table 4 Incidence and risk of dementia associated with acupuncture treatment and physical rehabilitation in patients with stroke

Acupuncture	Rehabilitation	n	Cases	Incidence*	HR	(95% CI)†
No	No	1816	327	35.9	1.00	(reference)
No	Yes	3794	698	34.1	0.90	(0.79 to 1.03)
Yes	No	1816	244	29.8	0.76	(0.64 to 0.90)
Yes	Yes	3794	476	25.0	0.64	(0.56 to 0.74)

*Per 1000 person-years.

†Adjusted for all covariates listed in table 1.

(such as the National Institutes of Health Stroke Scale or the Barthel Index), lesion characteristics such as location or size, biochemical measures, and patient lifestyle factors such as smoking, drinking alcoholic beverages and physical activity. Second, our study could not validate the actual acupuncture points used in treatment given the limited information provided by the National Health Insurance Research Database. Because acupuncture treatments for patients with stroke vary, we could not confirm that all traditional Chinese medicine physicians performed the same procedures or used the same acupuncture points. Finally, residual confounding is always possible, although we used propensity score matching procedure and multivariate regression adjustment for several potential confounding factors in our analysis.

To the best of our knowledge, our study is the first population-based study that rigorously evaluated the impact of acupuncture treatment on the risk of dementia in patients with stroke. We found that patients with non-haemorrhagic stroke receiving acupuncture treatment had a reduced risk of dementia. Although the beneficial effect of acupuncture on dementia risk was investigated in this study, future population-based studies that overcome the limitations of this study are needed to provide more evidence of this association.

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Competing interests None declared.

Patient consent To protect personal privacy, the electronic database was decoded with patient identification scrambled for further academic access for research. According to National Health Research Institutes regulations, informed consent is not required because of the use of decoded and scrambled patient identification.

Ethics approval This study was evaluated and approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB-201505055) and E-DA Hospital (EDA-JIRB-2014012).

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