

Acupuncture Decreases the Incidence of Post-stroke Dementia: A Taiwan Nationwide Retrospective Cohort Study

Shao-Ang Chu

E-Da Hospital

Te-Yuan Chen

E-Da Hospital

Po-Yuan Chen

E-Da Hospital

Wei-Jie Tzeng

E-Da Hospital

Cheng-Loong Liang

E-Da Hospital

Kang Lu

E-Da Hospital

Han-Jung Chen

E-Da Hospital

Chin-Chuan Tsai

E-Da Hospital

Hao-Kuang Wang (✉ ed101393@edah.org.tw)

Research

Keywords: Acupuncture, Post-stroke dementia, Incidence

Posted Date: July 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-39353/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

BACKGROUND

Stroke has been recognized as one of the major causes of adult disability worldwide, and post-stroke dementia may affect up to one-third of stroke survivors. This condition could be prevented if we could recognize and treat it earlier. Acupuncture as a complementary treatment for stroke has been shown to be beneficial for subsequent post-stroke rehabilitation. Our study investigated if acupuncture served additional advantages to decreasing the incidence of post-stroke dementia.

METHODS

We provide a retrospective cohort study from Taiwan National Health Insurance Research Database. This study compared the incidence of post-stroke dementia between cohorts with and without acupuncture treatment by calculating adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of acupuncture associated with post-stroke dementia using Cox proportional hazard regressions. The study group was composed of 9,547 patients who received first hospitalization for the treatment of stroke between 2002 and 2004; of which, 47,735 comparison patients were defined as the control group. The two groups were followed-up until the diagnosis of dementia presented or until the end of 2007.

RESULTS

The adjusted HRs of developing dementia among patients with stroke was 4.705 times the average (range, 4.353–5.085), and the incidence of dementia was higher in males. The study group tended to have less incidence of all kinds of dementia after acupuncture treatment, and patients without stroke receiving acupuncture had a lower probability of dementia than those untreated during the follow-up period.

CONCLUSIONS

This study presents evidence that acupuncture serves as an effective and alternative procedure to lower the risk of post-stroke dementia and the overall incidence of dementia in Taiwanese population.

Background

Stroke has been recognized as one of the major causes of adult disability worldwide. Survivors of stroke are at increased risk of developing cognitive impairment due to acute tissue damage. Assuredly, one-third of these survivors are found to have a significant degree of cognitive impairment within the first month after the event[1–3]. The lifetime risk of developing either stroke or dementia by age of 65 is one in three in men and one in two in women[4]. Post-stroke condition constitutes a well-defined reason of dementia

first recognized by Sir Thomas Willis in 1672 under the name postapoplectic dementia[2]. This is an etiological classification of dementia characterized by cognitive impairment as a result of ischemic or haemorrhagic stroke. Hypoperfusion and thromboembolism events lead to decreased cerebral blood flow, hypoxia, and oxidative stress and trigger inflammatory responses, subsequently damaging the area of brain important for memory, cognition, and behaviour[5]. Although functional recovery develops over the course of 26 weeks after a stroke, and physical impairments tend to improve to a greater or lesser degree, the survivors are often left with disabilities and worsening cognitive impairments[6, 7].

Currently there is no definitive and effective treatment for post-stroke dementia. Treatments with antioxidants, anti-inflammatory agents or agents increasing cerebral perfusion have not provided satisfactory results[8]. Numerous clinical studies and systemic reviews support the therapeutic effects of acupuncture in vascular dementia (VD) and post-stroke rehabilitation[9–11]. However, these therapeutic effects remain unclear because of poor methodology and small sample sizes[12, 13]. Acupuncture, with many categories such as manual acupuncture, electroacupuncture, laser acupuncture, and acupoint injection, serves as a form of alternative treatment and an essential component of traditional Chinese medicine which can be traced back 3,000 years[9]. It is a relatively safe procedure with few adverse effects. The mechanisms of acupuncture on VD are still uncertain; however, animal-based studies demonstrate the possibility of reducing oxidative stress, attenuating neuronal apoptosis, relieving neuroinflammation, regulating glucose metabolism, modulating neurotransmitters, and improving synaptic plasticity and blood vessel function[14]. Acupuncture has become universally accepted. The 2007 US National Health Interview Survey found 3.1 million adults and 150,000 children had received acupuncture in the previous year, and acupuncture use increased overall between 2002–2007[15, 16].

It is unknown if acupuncture is an adequate therapeutic method to reduce post-stroke dementia. Using the Taiwan National Health Insurance Research Database(NHIRD), we conducted a retrospective, nationwide population-based cohort study to investigate the possibility of acupuncture use in reducing incidence of post-stroke dementia.

Methods

Database

We conducted a retrospective, population-based cohort study of patients who are registered in the Longitudinal Health Insurance Database (LHID2000). 98.4% of the population in Taiwan (approximately 22.96 million) has been enrolled in Taiwan's NHIRD, which comprises healthcare data from the medical records of all beneficiaries[18, 19]. The LHID2000 is composed of 1 million insured subjects randomly selected from the NHIRD without bias to age and gender. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes (established according to the World Health Organization criteria) are included in the diagnostic data[17]. Details of the generation, monitoring, and maintenance related to the database are published online by the Taiwan's National Health Research Institutes (<http://nhird.nhri.org.tw/>)[18, 19].

Study sample

Patients with a diagnosis of stroke (ICD-9-CM code 430–437), receiving treatment in the hospital between January 1st, 2002 and December 31st, 2004 were enrolled in this study[18]. A flow chart of this study is shown in Fig. 1. We excluded patients aged younger than 40 to restrict the study to the assessment of the most common aetiology of stroke. In order to confirm that all patients with stroke enrolled in this study were incident cases, only new-onset stroke patients were included. Patients with the diagnosis of stroke or dementia before 2001 were excluded. Furthermore, patients who had the following conditions prior to the initial use of health care facilities were identified and excluded from this study: ICD-9-CM code 290.0 (senile dementia, uncomplicated); 290.1 (presenile dementia); 290.2 (senile dementia with delusional or depressive features); 290.3 (senile dementia with delirium); 290.4 (arteriosclerotic dementia); 294.1 (dementia in conditions classified elsewhere); 331.0 (Alzheimer's disease, AD); 331.1 (Pick disease); and 331.2 (senile degeneration of the brain). A total of 9,547 subjects who had strokes from 2002 to 2004 were matriculated in this study.

We built up a comparison cohort by extracting randomly from the records of the remaining patients in LHID2000 with identical exclusion criteria. The control group comprised 47,735 selected age- and sex-matched individuals without a previous history of stroke or dementia, such that the ratio of comparison subjects to stroke patients was 5:1.

Main outcome measures

We established the primary endpoint of this study as the occurrence of dementia in both genders during a 3-year period from the individuals' initial use of health care. Then, acupuncture (procedure code: B41, B42, B45, B46, P27041, P33031) data was collected to determine whether it is an effective treatment in reducing the incidence of post-stroke dementia. We also categorized the data for these dementia subtypes; AD (ICD-9-CM code 331.0), VD (ICD-9-CM code 290.4), and unspecified dementia (ICD-9-CM codes 290.0 to 290.4, 294.1, and 331.1 to 331.2).

Statistical analysis

Cases and controls were followed from the initial hospitalization date until December 31st in 2007. Pearson's chi-square test was administered to compare the baseline characteristics of the stroke cases receiving acupuncture and non-stroke controls from the NHIRD. Selected comorbidities were included if they occurred in either an inpatient setting or 3 or more ambulatory care claims that had been recorded 1 year before the initial ambulatory care visit. Multivariate Cox proportional hazard regression model was conducted to evaluate the hazard ratios (HRs) with 95% confidence intervals (CIs) for risk of dementia in patients receiving acupuncture after occurrence of stroke. Age, gender, and selected comorbidities were adjusted. Apart from the abovementioned comorbidities, we also adjusted for acupuncture in the regression modelling. A p value < 0.05 was defined as statistical significance in this study. The 5-years disease-free survival rate was evaluated with the Kaplan-Meier log rank test to examine differences

between cohorts. A statistical analysis software system (SAS, System for Windows, version 9.2, SAS Institute, Inc., Cary, NC, USA) was used to perform the statistical analyses.

Results

Overall, 9,547 and 47,735 patients were included in the stroke and non-stroke cohorts, respectively. There were no significant differences in age or gender between these groups. Geographic characteristics and comorbidities of the patients with stroke and comparison patients are shown in Table 1. The proportion of men was higher than that of women in both cohorts (53.48% vs. 46.52%). The mean age of the patients was 66.02 ± 11.72 years. After matching for age and gender, the comorbidities of diabetes, dyslipidaemia, hypertension, coronary heart disease, heart failure, atrial fibrillation, peripheral vascular disease, respiratory system, peptic ulcer disease, chronic liver disease, chronic kidney disease, rheumatologic disease, and cancer were more prevalent in the stroke cohort, compared with the non-stroke cohort.

Table 1
Geographic characteristics and comorbidities of the patients with stroke and comparison patients.

Characteristic	Patients With stroke (N = 9,547)		Comparison Patients (N = 47,735)		P
	N	%	N	%	
Gender					1.0000
Male	5,106	53.48	25,530	53.48	
Female	4,441	46.52	22,205	46.52	
Age, mean +-SD	66.0213 ± 11.7226		66.0213 ± 11.7221		1.0000
Age Group					1.0000
40–59	2,798	29.31	13,990	29.31	
60–74	4,261	44.63	4,261	44.63	
≥ 75	2,488	26.06	12,440	26.06	
Geographic region					< .0001
Northern	3,933	41.20	20,513	42.97	
Central	2,607	27.31	11,312	23.70	
Southern	2,568	26.90	13,654	28.60	
Eastern	291	3.05	1,573	3.30	
Missing	148	1.55	683	1.55	
Comorbidities					
Diabetes	3,157	33.07	7,985	16.73	< .0001
Dyslipidaemia	16	0.17	16	0.03	< .0001
Hypertension	7,189	75.30	18,654	39.08	< .0001
Coronary Heart Disease	3,317	34.74	8,210	17.20	< .0001
Heart Failure	879	9.21	2,109	4.42	< .0001
Atrial Fibrillation	399	4.18	559	1.17	< .0001
Peripheral Vascular Disease	874	9.15	1,725	3.61	< .0001

Chi-square test and t test

	Patients With stroke (N = 9,547)		Comparison Patients (N = 47,735)		
Respiratory System	2,308	24.18	8,176	17.13	< .0001
Peptic Ulcer Disease	3,069	32.15	10,442	21.87	< .0001
Chronic Liver Disease	2,004	20.99	7,054	14.78	< .0001
Chronic Kidney Disease	1,160	12.15	3,014	6.31	< .0001
Rheumatologic Disease	449	4.70	1,548	3.24	< .0001
Cancer	638	6.68	2,687	5.63	< .0001
Chi-square test and t test					

The crude and adjusted HRs of dementia among patients and controls in each gender group during a 3-year follow-up period from initial treatment are shown in Table 2. Compared to the patients in the control cohort, patients with stroke had significantly higher incidence of dementia (14.70% vs. 3.36%). The values of stroke patients were higher than corresponding values in the non-stroke cohort; 4.71 (95% CI, 4.35–5.07; $p < 0.001$) experienced dementia within the follow-up period according to Cox proportional hazard regressions (stratified by gender, age group, and the year of initial health care use). We further analysed the HRs according to gender after adjusting the data for the presence of comorbidities. The HRs acquired within the male group and female group were 5.40 (95% CI 4.84–6.04, $p < 0.001$), and 4.13 (95% CI 3.70–4.61, $p < 0.001$), respectively. Figure 2 indicates the disease-free survival curves determined using the Kaplan–Meier log rank analysis.

Table 2
Crude and adjusted HRs of dementia among patients and controls in each gender group during a 3-year follow-up period from initial treatment.

	Patients With stroke		Comparison Patients	
	N = 9,547		N = 47,735	
Dementia Occurrence	N.	%	N.	%
Total	1,403	14.70	1,604	3.36
Crude HR (95% CI)	4.818(4.484–5.176)		< .0001	
Adjusted HR (95%CI)	4.705(4.353–5.085)		< .0001	
Male	741	14.51	727	2.85
Crude HR (95% CI)	5.641(5.092–6.250)		< .0001	
Adjusted HR (95%CI)	5.404(4.839–6.035)		< .0001	
Female	662	14.91	877	3.95
Crude HR (95% CI)	4.134(3.737–4.573)		< .0001	
Adjusted HR (95%CI)	4.130(3.701–4.610)		< .0001	
Adjusted for age, gender, geographic region, and Charlson Comorbidity Index				

Table 3 shows the relative risk of developing distinct types of dementia after acupuncture treatment in the stroke patient group. The analysis consistently demonstrates that, compared to stroke patients without acupuncture, the study patients were less likely to sustain several subtypes of dementia during the 3-year follow-up period after their initial assessment. Notably, the adjusted HRs for other dementia in patients with acupuncture was 0.49 (95% CI, 0.41–0.59; $p < 0.001$). Figures 3 and 4 disclose the disease-free survival curves of the patients with stroke and comparison cohorts who did and did not undergo acupuncture using the Kaplan–Meier method.

Table 3
Relative risk of developing distinct types of dementia after acupuncture treatment in the stroke patient group.

	Patients With Acupuncture		Non- Acupuncture	
	N = 2,449		N = 7,098	
	N	%	N.	%
Total	183	7.47	1220	17.19
Crude HR (95% CI)	0.399 (0.341–0.466)		< .0001	
Adjusted HR (95%CI)	0.503 (0.430–0.589)		< .0001	
Alzheimer Disease	7	0.29	61	0.86
Crude HR (95% CI)	0.304(0.139–0.665)		0.0028	
Adjusted HR (95%CI)	0.400(0.181–0.883)		0.0233	
Vascular Dementia	41	1.67	216	3.04
Crude HR (95% CI)	0.503(0.360–0.702)		< .0001	
Adjusted HR (95%CI)	0.603(0.430–0.846)		0.0034	
Other Dementia	138	5.63	956	13.47
Crude HR (95% CI)	0.384(0.321–0.459)		< .0001	
Adjusted HR (95%CI)	0.490(0.409–0.587)		< .0001	
Adjusted for age, gender, geographic region, and Charlson Comorbidity Index				

The crude and adjusted HRs of dementia among patients with stroke and those who have received acupuncture in this study are shown in Table 4. Adjusted HR of dementia for patients with stroke was 4.79 (95% CI 4.44–5.18, $p < 0.001$) and surprisingly, the result reveals that patients who received acupuncture, whether they have a history of stroke or not, are at lower risk of developing dementia during this 3-year follow-up.

Table 4

Crude and adjusted HRs of dementia among patients with stroke and those who have received acupuncture.

	Crude (95% CI)	Adjusted HR (95%CI)
Total		
Stroke	5.039(4.690–5.414)*	4.793(4.435–5.181)*
Acupuncture	0.418(0.374–0.467)*	0.554(0.495–0.620)*
Regression Crude: independent var-Stroke and Acupuncture		
Regression Adjust: independent var- Stroke, Acupuncture, Age, Gender, Geographic region, and Charlson Comorbidity Index		
* p < .0001		

Discussion

The consequence of this retrospective, nationwide, population-based cohort study illustrates significant associations between post-stroke dementia and application of acupuncture. The best methods to prevent post-stroke dementia are to impede recurrence of stroke and reduce severity of stroke-related impairment through the most favourable acute treatment and intensive secondary prevention [20–22]. Secondary prevention consists of medical interventions and lifestyle modification. To date, advanced treatment for vascular risk factors and vascular disease may prevent post-stroke dementia. An observational study unveiled reduced cognitive impairment in patients with appropriate post-stroke vascular risk management, including antiplatelet therapy, antihypertensive drugs and statins, or anticoagulants, as indicated[21]. Furthermore, cognitive function can benefit from therapy for neuropsychiatric symptoms like depression, apathy, and anxiety, as well as cognitive training/stimulation[22]. According to our results, we suggest that early intervention with acupuncture could also decrease the risk of post-stroke dementia.

Acupuncture as a traditional Chinese healing technique treats disorders by inserting needles into specific acupoints, and it is generally considered safe when performed correctly. The use of acupuncture treatment for 43 diseases has been recommended by the World Health Organization[23], and as a non-pharmacological intervention, it is considered to be an alternative treatment for dementia[10–14]. In a recent animal study, improvement in cognition and hippocampal synaptic plasticity induced by acupuncture was achieved via activation of dopamine D1/D5 receptors[24].

After adjusting for geographic characteristics, region of residence and selected comorbidities, the proportion of men with diagnosis of stroke was a bit higher than that of women in both cohorts (53.48% vs. 46.52%) during this 3-year follow-up. The selected comorbidities were more prevalent in the stroke cohorts compared with the non-stroke cohorts. The mean age of the patients in the cohorts was 66.02 ± 11.72 years. In another study, older adults, residents in southern and eastern regions, patients with low insurance range, and antiplatelet use were prominent risk factors of post-stroke dementia in Taiwan[25].

We demonstrated that patients with stroke had significantly higher incidence of dementia rates within 3-year follow-up, and the incidence of dementia in male patients with stroke was higher than that of female patients with stroke. A pooled analysis of international data classified important contributors and risk factors to post-stroke dementia, and age over 65 and female gender are the mentioned risk factors[26, 27]. The mean age in our study and the result that stroke patients had higher incidence of dementia match with this analysis, however the effect of gender did not. Although there was no statistical significance, the proportion of male patients with diagnosis of stroke in our study was higher. Li CH et.al claimed that patients with stroke were at significantly more risk of dementia during the 5- and 10-year follow-up periods in Taiwan[25]. Post-stroke dementia is often recognized in the first weeks to months post-ictus, and thereafter, prevalence of post-stroke dementia increases with time[28]. Ethnic differences and a longer follow-up period should be considered.

The relationship between stroke and neurodegenerative diseases, such as AD and VD, has been established[1, 2–5]. VD is the second most common cause of cognitive decline, with only AD being more prevalent[29]. Multicellular interactions within the neurovascular unit, including damage to the blood-brain barrier, neuronal cell death or degeneration, glial reaction, and immune cell infiltration contribute to the aetiology[30]. Our results indicated stroke patients with subsequent acupuncture treatment were less likely to develop several subtypes of dementia during the 3-year follow-up. Notably, the adjusted HR for unspecified dementia in patients with acupuncture was 0.49 (95% CI, 0.41–0.59; $p < 0.001$). Pathological mechanisms of AD are poorly understood, and approximately 70% of the risk is believed to be inherited, with many genes being involved[31]. VD can also result from other conditions besides stroke that damage blood vessels and reduce circulation. This may explain why these most common aetiologies of dementia did not show statistical significance in our study, although there was a trend toward affirmative efficacy.

There is no obvious evidence to support any specific mechanism that contributes to the effect of acupuncture in decreasing the incidence of post-stroke dementia. Researchers have discovered that this therapy may reduce oxidative stress, attenuate neuronal apoptosis, relieve neuroinflammation, regulate glucose metabolism, modulate neurotransmitters, and improve synaptic plasticity and blood vessel function [14]. Interestingly, we discovered evidence that revealed that those patients who received acupuncture were at a lower risk of developing dementia regardless of whether they had the diagnosis of stroke or not. Patients who choose acupuncture as a complementary treatment may place more emphasis on personal health maintenance with regard to better knowledge and attitudes for disease prevention. These factors could also contribute to reduced incidence of dementia.

A retrospective, nationwide cohort was employed in our study, which provided a large sample size and more evidence compared to case-control or cross-sectional study designs. Problems like insufficient power and the effect of selection biases were minimized. However, our study had several limitations. First, the insurance claims data we collected lacked information regarding clinical risk scores (such as the National Institutes of Health Stroke Scale or the Barthel Index), characteristics of the lesion, its location, size, laboratory examination results, and factors of patients' lifestyle such as cigarette smoking, alcohol

consumption, and physical activity. Second, this study could not validate the actual acupoints used in the treatment of the stroke patients, as limited information is provided by the National Health Insurance Research Database. The acupoints chosen by traditional Chinese medicine physicians for stroke patients vary, and the beneficial effects are somewhat different[32]. Further studies need to be carried out to identify the protective effects against dementia from individual acupoints. Finally, residual confounding data is always present, even though we had utilized multivariate regression adjustments for several potential confounding factors in our analysis.

Conclusions

From the results of this nationwide retrospective cohort study, stroke patients with subsequent acupuncture treatment have a significantly lower risk of post-stroke dementia after adjustments for selective confounding factors. This study also showed that in general, patients treated with acupuncture had a lower risk of newly diagnosed dementia. The beneficial effect of acupuncture was investigated in our study, yet still very little is known regarding the mechanisms of acupuncture. Care must be taken in extrapolating from our results, and further investigations that overcome the limitations of this study are essential to ascertain the mechanisms for such effects and provide more evidence of the association.

List Of Abbreviations

HR, hazard ratio; CI, confidence interval; LHID2000, Longitudinal Health Insurance Database; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; AD, Alzheimer's disease; VD, Vascular dementia

Declarations

Ethics approval and consent to participate

We analyzed administrative claims data obtained from Taiwan's NHIRD. The details of database generation, monitoring, and maintenance are published online by the Taiwan's National Health Research Institutes (<http://nhird.nhri.org.tw/>). Because the National Health Insurance (NHI) program is the sole payer in Taiwan, the data represents the original medical claims for all islanders covered by the NHI program, and are distributed by sex, age, or amount of average payroll-related insurance payments. The subjects of this study were recruited by reviewing monthly patient discharge data released by NHIRD, and data in the NHIRD that could be used to identify patients is scrambled before being sent to the National Health Research Institutes(NHRI) for database construction. Because the analysis was limited to aggregate secondary data that could not be used to identify the patients, the study was approved by the NHRI Ethics Review Committee, Taiwan. However, the study protocol conformed to the ethical standards established by the Declaration of Helsinki (1964), which do not require written or verbal consent for data-linkage studies.

Consent to publish

Not applicable

Availability of data and materials

This retrospective, population-based cohorts were selected from among patients registered in the NHIRD, which was released for research purposes in 2008. The details of database generation, monitoring, and maintenance are published online by the Taiwan's NHRI (<http://nhird.nhri.org.tw/>)

Competing interests

The authors declare that they have no competing interests

Funding

This study was supported in part by grants from the E-da hospital, Kaohsiung, Taiwan (CFDR-B-103-1-2).

Authors' Contributions

SAC, CCT, and HKW designed research; SAC, TYC, PYC, WJT, CLL, KL and HJC analyzed data; SAC, CCT and HKW wrote the paper.

Acknowledgements

This study was supported by Center for Database Research, E-DA HEALTHCARE GROUP.

References

1. Gorelick PB, Nyenhuis D. Stroke and cognitive decline. *JAMA*. 2015;314(1):29–30.
2. Van Rooij FG, Kessels RP, Richard E, De Leeuw FE, van Dijk EJ. Cognitive impairment in transient ischemic attack patients: a systematic review. *Cerebrovasc Dis*. 2016;42(1–2):1–9.
3. Prince M, Guerchet M, Prina M. The epidemiology and impact of dementia: current state and future trends. Geneva: World Health Organization; 2015.
4. Henon H, Pasquier F, Leys D. Poststroke dementia. *Cerebrovasc Dis*. 2006;22:61–70.
5. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. *Exp Neurol*. 2015 Oct;272:97–108.
6. Lin Lu^{1,2}, Zhang Xiao-guang², Linda LD, Zhong¹, Zi-xian Chen², Yan Li², Guo-qing Zheng² & Zhao-xiang Bian¹ Acupuncture for neurogenesis in experimental ischemic stroke: a systematic review and meta-analysis *BMC Med*. 2017; 15: 11.

7. Seitz RJ, Donnan GA. Recovery potential after acute stroke. *Front Neurol.* (2015) 6:238.
8. Iadecola C. The pathobiology of vascular dementia. *Neuron.* 2013 Nov. 20.;80(4):844 – 66.
10. A systematic review of the effects of
Huang W, Kutner N, Bliwise DL. A systematic review of the effects of.
11. acupuncture in treating insomnia. *Sleep Med Rev.* 2009 Feb;13(1):73–104.
12. Shi GX, Liu CZ, Guan W, Wang ZK, Wang L, Xiao C, Li ZG, Li QQ, Wang LP. Effects of acupuncture on Chinese medicine syndromes of vascular dementia. *Chin J Integr Med.* 2014 Sep;20(9):661–6.
13. Shi GX, Li QQ, Yang BF, Liu Y, Guan LP, Wu MM, Wang LP, Liu CZ. Acupuncture for Vascular Dementia: A Pragmatic Randomized Clinical Trial. *ScientificWorldJournal.* 2015;2015:161439.
14. Wu P, Mills E, Moher D, et al. Acupuncture in poststroke rehabilitation: a systematic review and meta-analysis of randomized trials. *Stroke.* 2010;41:e171–9.
15. Zhang JH, Wang D, Liu M. Overview of systematic reviews and meta-analyses of acupuncture for stroke. *Neuroepidemiology.* 2014;42:50–8.
16. Ye Y, Zhu W, Wang XR, Yang JW, Xiao LY, Liu Y, Zhang X, Liu CZ. Mechanisms of acupuncture on vascular dementia-A review of animal studies. *Neurochem Int.* 2017 Jul;107:204–10.
17. Chon TY, Lee MC. Acupuncture *Mayo Clin Proc.* 2013;88:1141–6.
18. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: united States, 2007. *Natl Health Stat Report.* 2008;12:1–23.
19. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ.* 1976;54(5):541–53.
20. Feigin VL, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol.* 2013 Jan;12(1):53–64.
21. Gardner RC, Burke JF, Nettiksimmons J, et al. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol.* 2014;71:1490–7.
22. Pendlebury ST. Dementia in patients hospitalized with stroke: rates, time course, and clinico-pathologic factors. *Int J Stroke.* 2012;7(7):570–81.
23. Douiri A, McKeivitt C, Emmett ES, Rudd AG, Wolfe CD. Long-term effects of secondary prevention on cognitive function in stroke patients. *Circulation.* 2013;128(12):1341–8.
24. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst Rev.* 2012;2:CD005562.
25. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol.* 2008;85:355–75.
26. Ye Y, Li H, Yang JW, Wang XR, Shi GX, Yan CQ, Ma SM, Zhu W, Li QQ, Li TR, Xiao LY, Liu CZ. Acupuncture Attenuated Vascular Dementia-Induced Hippocampal Long-Term Potentiation Impairments via Activation of D1/D5 Receptors. *Stroke.* 2017 Apr;48(4):1044–51.
27. Li CH, Chang YH, Chou MC, Chen CH, Ho BL, Hsieh SW, Yang YH. Factors of post-stroke dementia: A nationwide cohort study in Taiwan. *Geriatr Gerontol Int.* 2019 Aug;19(8):815–22.

28. Pasquier F, Hénon H, Leys D. Risk factors and mechanisms of post-stroke dementia. *Rev Neurol.* 1999;155(9):749–53.
29. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* 2009;8:1006–18.
30. Mijajlović MD, Pavlović A, Brainin M, Heiss WD, Quinn TJ, Ihle-Hansen HB, ... Bornstein NM. Post-stroke dementia - a comprehensive review. *BMC Med.* 2017;15(1):11.
31. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham study. *Lancet.* 2007;3:1106–14.
32. Cai W, Zhang K, Li P, Zhu L, Xu J, Yang B, Hu X, Lu Z, Chen J. Dysfunction of the neurovascular unit in ischemic stroke and neurodegenerative diseases: An aging effect. *Ageing Res Rev.* 2017 Mar;34:77–87.
33. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet.* 2011 Mar;19(9770):1019–31. 377(.
34. Shih CC, Hsu YT, Wang HH, et al. Decreased risk of stroke in patients with traumatic brain injury receiving acupuncture treatment: a population-based retrospective cohort study. *PLoS One.* 2014 Feb 19;9(2):e89208.

Figures

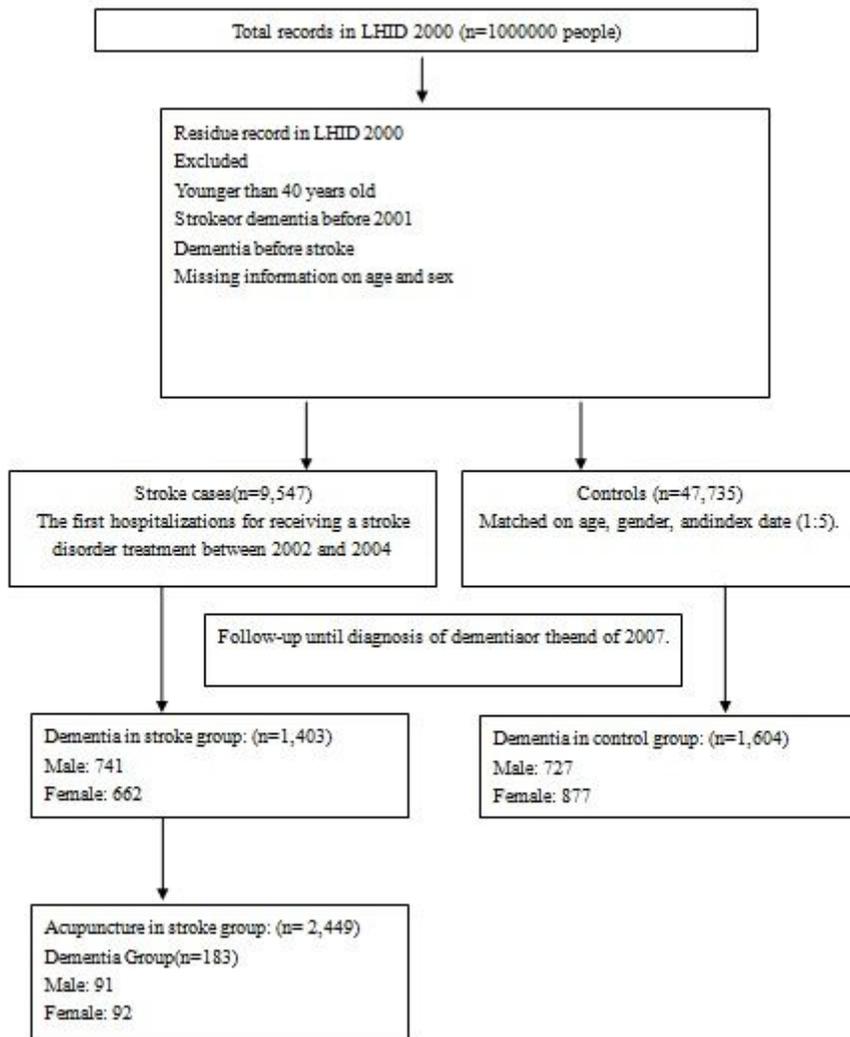


Figure 1

Flow chart of the study population.

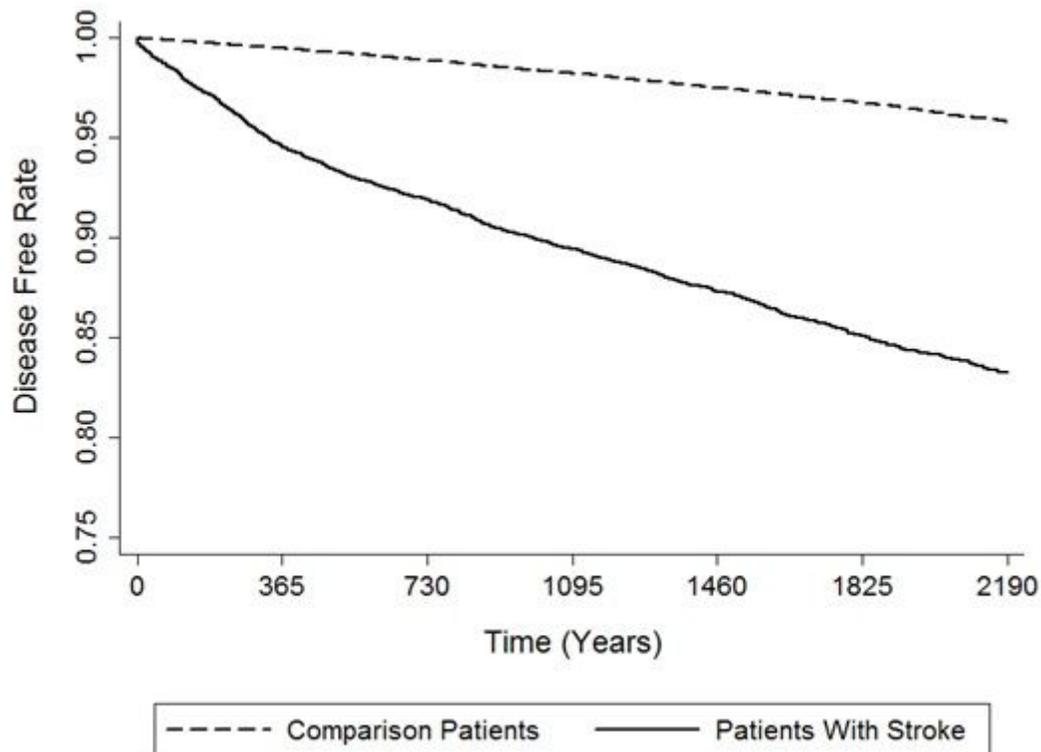


Figure 2

Indicates the disease-free survival curves determined using the Kaplan–Meier log rank analysis.

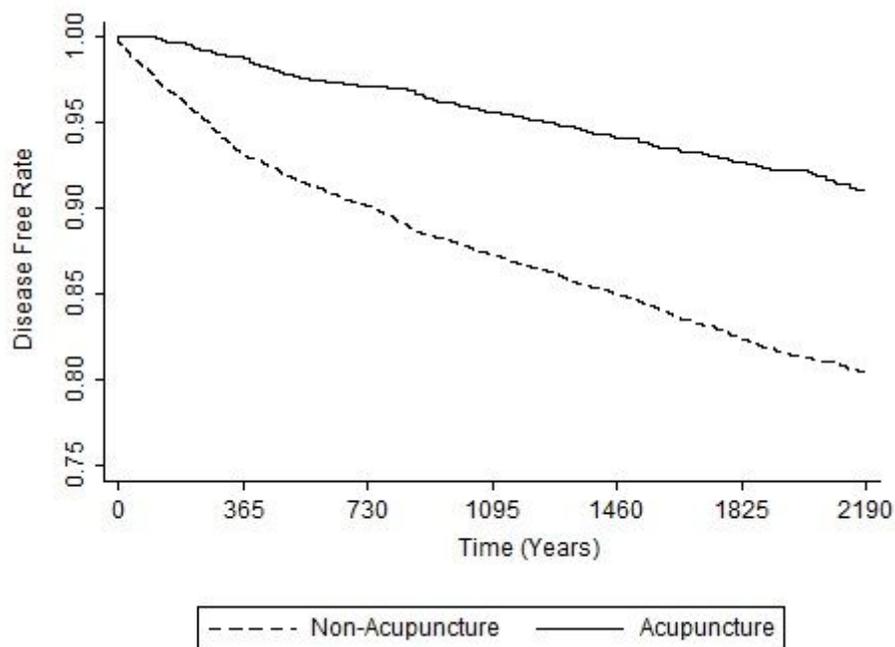


Figure 3

Kaplan-Meier curve of the estimated dementia-free proportions of patients with stroke who received and did not receive acupuncture treatment.

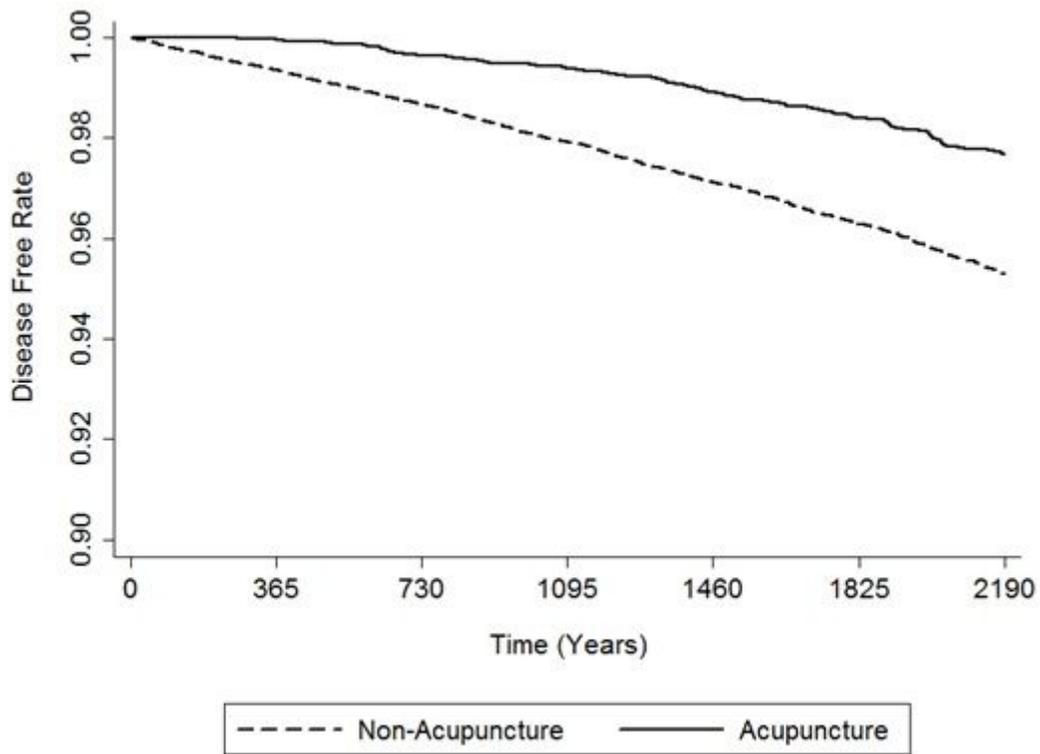


Figure 4

Kaplan-Meier curve of the estimated dementia-free proportions of non-stroke patients who received and did not receive acupuncture treatment.