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ORIGINAL RESEARCH

Acupuncture Treatment Reduced the Risk of Coronary Heart Disease in Patients with Depression: A Propensity-Score Matched Cohort Study

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Background: Major depressive disorder is a significant public health concern, which often leads to loss of productivity, functional decline, and various complications. The aim of this study was to investigate the effectiveness of acupuncture in the risk reduction of coronary heart disease (CHD) in patients with depression.

Methods: We enrolled patients diagnosed with depression between January 1, 1997, and December 31, 2010, through the Taiwanese National Health Insurance Research Database (NHIRD). Propensity score was used to match equal numbers (n=14,647) of acupuncture cohort and no-acupuncture cohort based on characteristics including sex, age, baseline comorbidity and medication. Patients were followed up until December 31, 2013, or withdrawn from the NHIRD. The Cox regression model was used to compare the hazard ratios (HRs) of CHD in the two cohorts.

Results: The basic characteristics of the two groups were similar. A lower cumulative incidence of CHD was noted in the acupuncture cohort (Log rank test, p < 0.001). Over time, 1626 patients in the acupuncture cohort (21.05 per 1000 person-years) and 2412 patients in the no-acupuncture cohort (39.84 per 1000 person-years) developed CHD (adjusted HR=0.50, 95% CI 0.47–0.53). The decreased CHD incidence was independent of age, sex, comorbidities, and medications used. The cumulative incidence of CHD was significantly lower in the acupuncture cohort than in the no-acupuncture cohort (Log rank test, p<0.001).

Conclusion: The results provided a real-world evidence that acupuncture may have beneficial effect on CHD risk reduction in patients with depression.

Keywords: acupuncture, depression, coronary heart disease, National Health Insurance Research Database, real-world evidence

Introduction

Major depression is the third cause of burden of disease worldwide and will rank first by 2030.[1] Moreover, depression poses significant impact on quality of life and carries a risk for heart disease[2] and stroke.[3] Acupuncture is a traditional Chinese intervention for disease treatment and has been practiced for thousands of years.[4] Patients with injury, musculoskeletal diseases, and neurological diseases represent the majority who receive acupuncture treatment.[5,6]

Patients with depression have a higher risk of coronary heart disease (CHD).[7] Depression is also a debilitating comorbidity of heart failure.[8] There have been a couple possible mechanisms to explain the link between depression and CHD.

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Depression is associated with the abnormal secretion of neurotransmitters, including serotonin, norepinephrine and dopamine.[9] Abnormal platelet physiology and pro-inflammatory factors have been suggested as potential factors leading to CHD.[10] Dysfunction of platelets by high concentrations of serotonin is one of the explanation.[11] The population attributable risk of CHD in people with depression was reported to be 32.5%, which is higher than other risk factors (eg, obesity: 20%, hypertension: 17.9%).[12] The hazard ratio (HR) of all-cause mortality of CHD was 1.16 in patients with depression.[13]

Selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), serotonin antagonists and reuptake inhibitors (SARIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and monoamine oxidase inhibitors (MAOIs) are common antidepressant medications.[14] TCAs have cardiac toxicity, and SNRIs have complications related to hypertension.[15,16] Patients should be closely observed when they have these prescriptions. There is no evidence that shows that patients with depression have a reduced risk of CHD with the other antidepressants. Thus, clinical doctors have a great interest in finding a treatment not only for treating depression but also for reducing CHD risk. SSRIs have been recommended by the American Heart Association (AHA) for treating CHD patients with depression because of their safety.[17] Although some studies have shown the effectiveness of acupuncture in patients with depression,[18,19] less evidence could be found from long-term follow-up studies to show that patients with depression have CHD protection with acupuncture treatment. The National Health Insurance (NHI) program was established in 1995 in Taiwan by the National Health Insurance Administration.[20] Since 1996, traditional Chinese medicine (TCM) services have been reimbursed through the NHI program, which covers more than 99% of the Taiwanese population.[21,22] All of the claims data were de-identified and then stored in the Taiwanese National Health Insurance Research Database (NHIRD) for research purpose.[20] The large-scale real-world data without sampling bias is one of the advantages of this database.[23] In this study, we aimed to determine if patients with depression could have lower CHD risk when they received acupuncture therapy. Samples of one million people in the NHIRD were randomly selected and enrolled in the study for further investigation.

Materials and Methods
Data Sources
A nationwide, population-based, 1:1 propensity score-matched cohort study by Insurance Database 2000,[21,24,25] which contains all of the original claims data of 1 million beneficiaries randomly sampled from the registry of all beneficiaries in 2000, was our data source.[22] There was no significant difference in our sample and the general population in age, sex, birth year, or average insured payroll-related costs. Diagnosis was coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Informed consents were waived because these were de-identified secondary data from the NHIRD. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Study Cohort Identification
We identified 55,176 patients who were newly diagnosed with depression (ICD-9-CM codes 296.2–296.3, 300.4 and 311) from 1 January 1997 to 31 December 2010 (Figure 1). Patients younger than 18 years, patients with incomplete data on age and sex during the follow-up period were excluded. Patients received acupuncture therapies from the initial diagnosis of depression through 31 December 2010 were included in the acupuncture cohort; those who did not accept acupuncture therapy during the same follow-up period were defined as no-acupuncture cohort. We included 43,395 patients, 18,912 patients in the acupuncture cohort and 24,483 patients in the no-acupuncture cohort. Random selection was performed using a 1:1 propensity score match to minimize the differences in the basic data, and the number of participants in each cohort was 14,647. Propensity score approaches were processed to minimize confounding by the indication of acupuncture therapy. One to one propensity score matching was conducted by sex, age, comorbidities, and prescription medications through multiple logistic regression analysis.[26] Eventually, the numbers of participants in the acupuncture and no-acupuncture cohorts were the same. Immortal time was the period between the first acupuncture therapy and the date of initial diagnosis with depression. Patients were followed up until December 31, 2013, or withdrawn from the NHIRD.

Covariate Assessment
Age and sex are the sociodemographic factors. We divided patients into three groups by to age (18–39 years, 40–59 years, and ≥60 years). Comorbidities, such as diabetes

mellitus (DM; ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (CHF; ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), alcoholism or alcohol-related disorders (ICD-9-CM codes 291, 303, 305.00–305.03, 790.3, and V11.3), tobacco dependence (ICD-9-CM code 305.1), and obesity (ICD-9-CM codes 278 and A183) were taken into consideration when ICD-9-CM codes appeared more than 1 time in outpatient or inpatient records before the primary diagnosis of depression. The drugs used included nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, statins, SSRIs (escitalopram, fluvoxamine, sertraline), MAOIs (selegiline, isocarboxazid, tranylcypromine, phenelzine, moclobemide), TCAs (amoxapine, desipramine, imipramine, doxepin, clomipramine, trimipramine) and other antidepressants (SNRIs: venlafaxine, duloxetine, milnacipran; NDRI: bupropion; SARI: mesyrel; NaSSA: mirtazapine), which were collected after initial diagnosis of depression.[27] Among the conventional medication for depression, agomelatine is one of the FDA-approved medications for depression treatment. It is a melatonergic agonist and 5HT2c antagonist that could improve sleep patterns and the release of norepinephrine and dopamine.[28] However, agomelatine was not reimbursed by the National Health Insurance program in Taiwan until 2012, therefore it was not included in our study.

Types of Acupuncture and Disease Categories in the Acupuncture Cohort

Acupuncture types were identified by the treatment codes, including manual acupuncture of TCM type (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, P32103, and P33031) and electroacupuncture (B43, B44, B86, B87, B88, B89, and P33032). We classified disease categories for patients with depression accepted acupuncture therapy by ICD-9-CM codes. When patients had treatment course of acupuncture, more than one ICD-9-CM code may be found that numbers of total participants were more than acupuncture cohort only.

Outcome Measurement

The index date was defined as the first time that the patients started to receive acupuncture and the immortal time was defined as the period from the initial diagnosis of depression to the index date. The occurrence of CHD (ICD-9-CM code: ICD-9-CM: 410.9, 411.1, 413, 414.0, 414.8 and 414.9) after the index date was measured. The outcome measurement was the comparison of incidences of CHD in the two cohorts with the variable of comorbidities and drug used before the end of the study (December 31, 2013).

Statistical Analyses

Baseline characteristics of the acupuncture and no-acupuncture cohorts were compared by standardized mean differences (SMD). Negligible difference in mean values or proportions between the two cohorts was defined as less than 0.1 standard deviation (SD). HR and 95% confidence interval (CI) were calculated for each variable item by Cox proportional hazards regression. Kaplan–Meier method and the logrank test were conducted to find the difference between two cohorts in the development of CHD. Individuals were censored at death, loss of follow-up, withdrawal from the insurance system, or the end of 2013, whichever came first. Statistical analysis and figures were performed by SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$ in two-tailed tests.

Results

Random selection was performed using a 1:1 propensity score match to minimize the differences in the basic data, and the number of participants in each cohort was 14,647 (Figure 1).

Table 1 shows the baseline characteristics of both cohorts. The distributions of sex, age, comorbidities, and prescription in these two cohorts were similar. Female participants were the majority in both cohorts, and most patients were between 40 and 59 years old. Hypertension was the most common comorbidity; more than 20% of patients had this problem. In the patients with depression, 12% had DM, 19% had hyperlipidemia, and 1% had CHF and 1% had anxiety. There was no difference in the proportions of alcoholism or alcohol-related disorders, tobacco dependence, and obesity in the two cohorts. NSAIDs were most common medications in both cohorts, and almost all patients had this prescription. Of the participants in these cohorts, 76% used oral steroids, 17% had statin agents, 62% were treated by SSRIs, 8% had MAOIs prescriptions and 34% received TCAs treatment. Manual
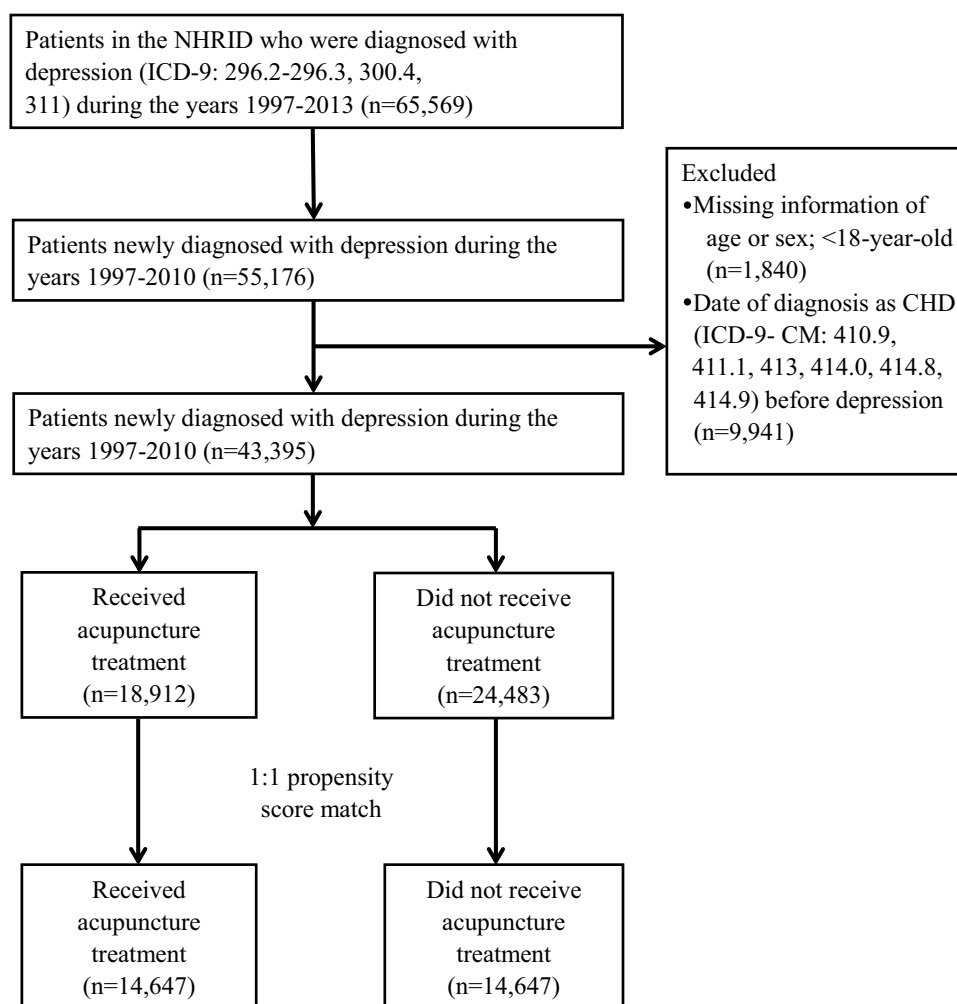
Figure 1 A total of 43,395 patients with depression were newly diagnosed from 1997 to 2010. Sex, age, comorbidities, and prescription drugs used were processed via propensity-score matching 1:1 by 14,647 patients who were included in both the acupuncture cohort and the no-acupuncture cohort.
Abbreviation: LHID 2000, Longitudinal Health Insurance Database 2000.

acupuncture was the most common manipulation, and 88% of the patients had this experience.

Electroacupuncture was performed in 3% of the participants. Another 9% of patients were treated by combination of acupuncture with their prescriptions. The mean duration between when the patients had been diagnosed with depression and the first time receiving acupuncture therapy was approximately 1320 days. The mean number of acupuncture visits was 8.71.

A total of 4038 patients developed CHD events during the follow-up period (Table 2). Patients with depression had a lower risk of developing CHD after they received acupuncture treatment, and the adjusted HR was 0.47 (95% CI 0.44–0.51). Figure 2 shows that the cumulative incidence of CHD was significantly lower in the acupuncture cohort (log-rank test, p < 0.001).

Table 3 shows the 1626 patients in the acupuncture cohort (21.05 per 1000 person-years) and 2412 patients in the no-acupuncture cohort (39.84 per 1000 person-years) who developed CHD (adjusted HR 0.50, 95% CI 0.47–0.53). The benefit for lowering CHD incidence was observed in male and female groups: the adjusted HR was 0.47 in females, 95% CI 0.43–0.51; adjusted HR was 0.56 in males, 95% CI 0.50–0.62. The effectiveness of acupuncture therapy could also be found in different age groups (adjusted HR 0.53, 95% CI 0.45–0.62 in the 18–39-year-old group; adjusted HR 0.48, 95% CI 0.44–0.52 in the 40–59-year-old group; adjusted HR 0.54, 95% CI 0.47–0.62 in the over 60-year-old group). Whether they were patients with comorbidities or not, acupuncture therapy was helpful for decreasing the risk of CHD. Coprescription with steroids, NSAIDs

Table 1 Characteristics of Patients with Depression Who Received Acupuncture Therapy and Patients with Depression Who Did Not Receive Acupuncture Therapy

Variable	Accepted Acupuncture				Standardized Mean Difference
	No (n =14,647)		Yes (n =14,647)		
	n	%	n	%	
Gender					0.4746
Women	9295	63.46	9236	63.06	
Men	5352	36.54	5411	36.94	
Age group					0.99
18–39	6630	45.27	6630	45.27	
40–59	6652	45.42	6652	45.42	
≥60	1365	9.32	1365	9.32	
Mean±SD (years)	43.19 (14.86)		43.20 (14.81)		0.9427
Baseline Comorbidity					
Diabetes mellitus	1746	11.92	1779	12.15	0.5534
Hypertension	3262	22.27	3384	23.1	0.0888
Hyperlipidemia	2783	19	2752	18.79	0.6436
Congestive heart failure	169	1.15	175	1.19	0.7449
Anxiety	107	0.73	101	0.69	0.6763
Alcoholism	274	1.87	261	1.78	0.5705
Tobacco used	104	0.71	104	0.71	0.99
Obesity	130	0.89	125	0.85	0.7532
Drug used					
Oral steroids	11,108	75.84	11,131	76	0.7533
NSAIDs	14,516	99.11	14,516	99.11	0.99
Statins	2534	17.3	2534	17.3	0.99
SSRIs	9095	62.09	9035	61.68	0.4704
MAOIs	1179	8.05	1162	7.93	0.7141
TCAs	4999	34.13	4999	34.13	0.99
Other antidepressant drugs	4757	32.48	4653	31.77	0.1932
Types of acupuncture					
Manual acupuncture	–	–	12,842	87.68	
Electroacupuncture	–	–	418	2.85	
Combination of manual acupuncture and electroacupuncture	–	–	1387	9.47	
Duration between depression date and index, days (mean, median)	1315.98 (1031)		1322.59 (979)		
Acupuncture visits, (mean, median)			8.71 (3)		

Note: The mean (median) of follow-up period were 4.13 (3.35) and 5.27 (4.59) years for acupuncture cohort and compared cohort.
Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants.

or statins did not change the positive results of acupuncture therapy. With the help of acupuncture treatment, lower CHD risk could still be found in patients prescribed different types of antidepressant medications. Table 4 also reveals depression patients had lower incidence of developing CHD (estimate subhazard ratio 0.52, 95% CI 0.49–0.56) through competing-risks regression models.[29]

Discussion

This is the first study to demonstrate that the CHD risk in depression patients could be improved by acupuncture

Table 2 Cox Model with Hazard Ratios and 95% Confidence Intervals of Coronary Heart Disease Associated with Receiving Acupuncture and Covariates Among Patients with Depression

Variable	No. of Event (n=4038)	HR	(95% CI)	p-value
Accepted Acupuncture				
No	2412	1.00	reference	
Yes	1626	0.47	(0.44–0.51)	<0.0001

Note: HR represented relative hazard ratio.
Abbreviations: HR, hazard ratio; CI, confidence interval.

treatment. Mental disorders, which included depression, is one of the common disease categories among acupuncture visits in Taiwan.[6] The risk of CHD has never been mentioned as a result of acupuncture therapy in patients with depression. According to our results, more than half of the patients with depression have received acupuncture therapy in Taiwan. With the analysis of this real-world data with long-term follow-up, we were able to show that the benefit of acupuncture intervention was independent of sex, age, comorbidities and drugs use (oral steroids, NSAIDs, statins and SSRIs).
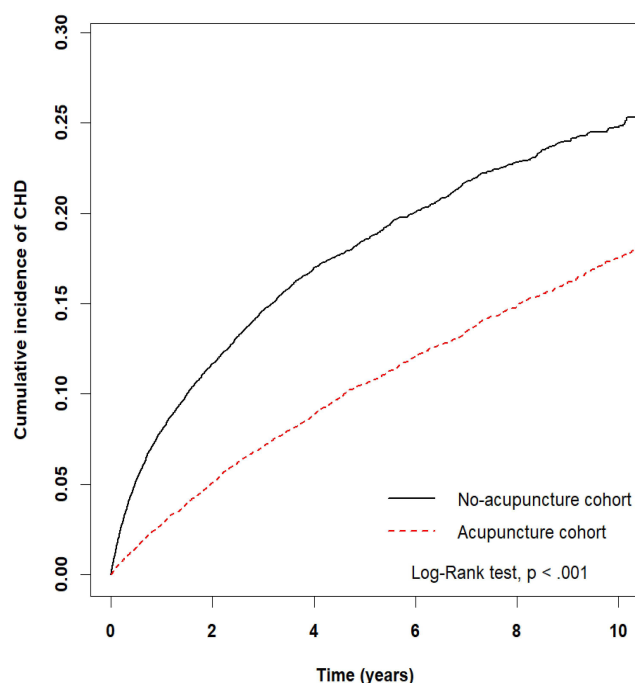

Figure 2 Cumulative incidence of coronary heart disease in acupuncture (dashed line) and the no-acupuncture cohort (solid line). Patients in acupuncture group had lower incidence of CHD significantly (Log rank test, p < 0.001).
Abbreviation: CHD, coronary heart disease.

A couple mechanisms might explain why acupuncture exerts protective effect in reducing the risk of CHD in patients with depression. An earlier study reported that acupuncture have advantages in left ventricular function in patients with coronary artery disease.[30] Recently, acupuncture was also demonstrated to be effective and safe in reducing frequency of angina attacks in patients with chronic stable angina.[31] Symptoms of depression are associated with several neurotransmitters, such as serotonin, norepinephrine and dopamine.[9] Serotonin is a vasoactive substance that has been identified in the brain, colon, and platelets.[32] In the cardiac system, it has also been noted in the vascular beds and sympathetic nerve. Serotonin is important in the pathophysiology of atherosclerosis because it can promote platelet aggregation and arterial vasoconstriction.[33–35] Stimulation via acupuncture might be able to regulate the serum level of serotonin.[36] Another hypothesis is that dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis contributes to depression. Stimulating hypothalamic and hippocampal regions by acupuncture has been shown to be helpful for stabilizing the HPA axis and normalizing the secretion of neurotransmitters.[37]

Vascular endothelial growth factor (VEGF) is a cellular mitogen. Its role in hippocampal neurogenesis is believed to be a response to stress. Some studies have found a relationship between VEGF and depression, and suggest that VEGF may be a new target for the treatment of depression.[38] Endothelial progenitor cells (EPCs) have beneficial effects in atherosclerosis, angiogenesis, and vascular repair. The effects of acupuncture on EPCs in patients with coronary heart disease through the VEGF pathway has been reported.[39] The regulation of VEGF may be a possible mechanism to prevent CHD in depression patients with acupuncture therapy, and further evaluations are warranted to provide more rigorous evidence.

Sleep problems, such as sleep apnea and short sleep duration, could contribute to CHD.[40,41] Improvement of sleep disturbance is beneficial for the management of depression, as demonstrated by the effectiveness of agomelatine.[28] Treatment of sleep disorders is also an indication of acupuncture therapy,[42,43] and this implies that acupuncture therapy may have indirect effects on the prevention of CHD in patients with depression.

Not only CHD but also comorbidities of depression, including DM, hypertension and CHF, have relationships with inflammation.[44,45] Acupuncture has been found to not only exert anti-nociceptive effect but also suppress

Table 3 Incidence Rates, Hazard Ratios and Confidence Intervals of Coronary Heart Disease for Patients with Depression Who Received and Did Not Receive Acupuncture, Stratified by Sex, Age, Comorbidities and Prescription Drugs Used

Variables	Accepted Acupuncture						Compared with No-Acupuncture Users	
	No			Yes			Crude HR	Adjusted HR[†]
	(n=14,647)			(n=14,647)				
	Event	Person Years	IR	Event	Person Years	IR	(95% CI)	(95% CI)
Total	2412	60,539	39.84	1626	77,231	21.05	0.56 (0.53–0.60)***	0.50 (0.47–0.53)***
Gender								
Women	1569	37,945	41.35	987	48,220	20.47	0.52 (0.48–0.57)***	0.47 (0.43–0.51)***
Men	843	22,594	37.31	639	29,010	22.03	0.62 (0.56–0.69)***	0.56 (0.5–0.62)***
Age group								
18–39	356	29,622	12.02	239	35,310	6.77	0.58 (0.49–0.68)***	0.53 (0.45–0.62)***
40–59	1615	26,805	60.25	1038	35,337	29.37	0.52 (0.48–0.56)***	0.48 (0.44–0.52)***
≥60	441	4112	107.24	349	6584	53.01	0.56 (0.49–0.65)***	0.54 (0.47–0.62)***
Baseline Comorbidity								
Diabetes mellitus								
No	1884	54,457	34.60	1225	68,358	17.92	0.54 (0.51–0.59)***	0.49 (0.45–0.52)***
Yes	528	6082	86.81	401	8873	45.20	0.57 (0.5–0.65)***	0.54 (0.47–0.61)***
Hypertension								
No	1305	49,451	26.39	831	60,307	13.78	0.54 (0.5–0.59)***	0.5 (0.46–0.55)***
Yes	1107	11,088	99.84	795	16,924	46.98	0.52 (0.47–0.57)***	0.5 (0.45–0.55)***
Hyperlipidemia								
No	1552	50,827	30.53	1043	64,033	16.29	0.56 (0.52–0.61)***	0.5 (0.46–0.54)***
Yes	860	9712	88.55	583	13,198	44.17	0.54 (0.48–0.6)***	0.48 (0.44–0.54)***
Congestive heart failure								
No	2341	60,116	38.94	1583	76,471	20.70	0.56 (0.53–0.6)***	0.5 (0.47–0.54)***
Yes	71	423	167.70	43	759	56.62	0.38 (0.26–0.56)***	0.44 (0.29–0.65)***
Anxiety								
No	2391	60,145	39.75	1609	76,745	20.97	0.56 (0.52–0.59)***	0.50 (0.47–0.53)***
Yes	21	394	53.28	17	486	34.97	0.73 (0.39–1.4)	0.69 (0.34–1.37)
Alcoholism								
No	2383	59,525	40.03	1609	75,941	21.19	0.56 (0.53–0.60)***	0.50 (0.47–0.54)***
Yes	29	1014	28.59	17	1290	13.18	0.48 (0.26–0.87)*	0.37 (0.20–0.69)**
Tobacco used								
No	2403	60,253	39.88	1622	76,918	21.09	0.56 (0.53–0.60)***	0.50 (0.47–0.53)***
Yes	9	286	31.46	4	312	12.80	0.41 (0.13–1.32)	0.22 (0.05–0.90)*
Obesity								
No	2390	60,134	39.74	1614	76,604	21.07	0.56 (0.53–0.60)***	0.50 (0.47–0.54)***
Yes	22	405	54.29	12	627	19.14	0.39 (0.19–0.79)**	0.19 (0.08–0.46)***
Drug used								
Oral steroids								
No	792	12,161	65.13	457	15,765	28.99	0.49 (0.43–0.55)***	0.43 (0.39–0.49)***
Yes	1620	48,378	33.49	1169	61,466	19.02	0.59 (0.55–0.64)***	0.54 (0.50–0.58)***

(*Continued*)

Table 3 (Continued).

Variables	Accepted Acupuncture						Compared with No-Acupuncture Users	
	No			Yes			Crude HR	Adjusted HR[†]
	(n=14,647)			(n=14,647)				
	Event	Person Years	IR	Event	Person Years	IR	(95% CI)	(95% CI)
NSAIDs								
No	54	241	223.91	38	399	95.32	0.52 (0.34–0.78)**	0.33 (0.21–0.53)***
Yes	2358	60,298	39.11	1588	76,832	20.67	0.56 (0.52–0.59)***	0.50 (0.47–0.54)***
Statins								
No	1971	48,983	40.24	1269	62,868	20.19	0.53 (0.50–0.57)***	0.47 (0.44–0.5)***
Yes	441	11,555	38.16	357	14,363	24.86	0.67 (0.58–0.77)***	0.64 (0.55–0.73)***
SSRIs								
No	1406	21,736	64.69	842	29,929	28.13	0.47 (0.43–0.51)***	0.44 (0.40–0.48)***
Yes	1006	38,803	25.93	784	47,302	16.57	0.66 (0.60–0.73)***	0.58 (0.53–0.64)***
MAOIs								
No	2163	54,822	39.45	1451	70,156	20.68	0.56 (0.52–0.59)***	0.50 (0.47–0.53)***
Yes	249	5717	43.56	175	7075	24.73	0.59 (0.49–0.72)***	0.53 (0.44–0.65)***
TCAs								
No	1505	38,617	38.97	962	48,656	19.77	0.54 (0.50–0.59)***	0.47 (0.44–0.51)***
Yes	907	21,921	41.37	664	28,574	23.24	0.59 (0.53–0.65)***	0.55 (0.49–0.60)***
Other antidepressant drugs								
No	2092	40,405	51.78	1379	53,621	25.72	0.53 (0.50–0.57)***	0.49 (0.45–0.52)***
Yes	320	20,134	15.89	247	23,610	10.46	0.67 (0.57–0.79)***	0.61 (0.52–0.72)***

Notes: Adjusted HR[†]: adjusted for accepted acupuncture, age, gender, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, anxiety, alcoholism, tobacco used, obesity, oral steroids, NSAIDs, statins, SSRIs, MAOIs, TCAs and other antidepressant drugs in Cox proportional hazards regression. * p<0.05; ** p<0.01; *** p<0.001.
Abbreviations: IR, incidence rate (per 1,000 person-years); HR, hazard ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants.

Table 4 Accepted Acupuncture Cohort to No-Acupuncture Cohort Subhazard Ratio of Coronary Heart Disease Estimated Using the Competing-Risks Regression Models

	Competing-Risks Regression Models	
	Accepted Acupuncture	
	No	Yes
Coronary heart disease		
Crude SHR (95% CI)	1 (Reference)	0.57 (0.54, 0.61)***
Adjusted SHR[†] (95% CI)	1 (Reference)	0.52 (0.49, 0.56)***

Notes: Crude SHR, relative subhazard ratio; Adjusted SHR[†]: multivariable analysis included age, gender, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, anxiety, alcoholism, tobacco used, obesity, oral steroids, NSAIDs, statins, SSRIs, MAOIs, TCAs and other antidepressant drugs. ***p<0.001.
Abbreviations: SHR, subhazard ratio; CI, confidence interval.

inflammation.[46–48] Through the release of calcitonin gene-related peptide, vasodilatory and anti-inflammatory effects were hypothesized to be induced by acupuncture.[49] Furthermore, cardiac work capacity could be improved by acupuncture in patients with angina pectoris.[50] Researchers also found that acupuncture pretreatment could inhibit the β1-adrenoceptor signaling pathway, an effect which protects the heart from myocardial ischemia injury in animal studies.[51] The potential of acupuncture to protect against CHD can be found in these studies, although further investigations are needed to determine whether these mechanisms are suitable for humans.

Our study has several limitations. The claim data from NHIRD could not be validated and the severity of depression, such as suicidal ideations and social and work disability were not included. Thus, we performed a 1:1 propensity score match, which was useful to minimize the difference between two cohorts. The percentages of patients prescribed antidepressants were similar. Personal habits and some

characteristics, such as height, weight, exercise status, smoking and drinking consumption, are difficult to identify from the NHIRD. Thus, we tried to define a diagnosis of alcoholism or alcohol-related disorders, tobacco dependence, and obesity to represent these parameters then via a 1:1 propensity score match to eliminate the difference. The distribution of patients with these problems was similar, and these comorbidities did not change the significant protective effect of acupuncture on CHD in patients with depression. The NHIRD database did not reveal the acupoints for depression treatment. And the dose of acupuncture therapy, such as frequency or duration is variable and depends on the diagnosis of the patients and the experience of the TCM doctors. Based on uniform TCM program training in Chinese medical colleges in Taiwan, most TCM doctors have basic ideas for treatment goals. But, different complaints, comorbidities and acceptance of patients could contribute to variable prescriptions of acupuncture. A retrospective study through real-world data could not offer the causal relation between acupuncture intervention and outcomes or collect adequate number of participants with same treatment course for analysis.[52]

Conclusions

The results of this study on CHD risk reduction demonstrate the effects and suggest advantages of acupuncture treatment in patients with depression in Taiwan. It provides noteworthy ideas for future studies to investigate the effectiveness of acupuncture to integrate to the clinical management of patients with depression.

Data Sharing Statement

The datasets we used in this study were released by the Taiwan NHIRD (http://nhird.hri.org.tw/en/indx.html), maintained and managed by National Health Research Institutes (http://www.nhri.org.tw/), Taiwan. The datasets are limited to be used for research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p= 987) and related regulations of National Health Insurance Administration and National Health Research Institutes, and the agreement must be signed by the applicant and his/her supervisor upon application submission. All applications are reviewed for approval of data release.

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.

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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