Acupuncture Treatment is Associated with a Decreased Risk of Dementia in Patients with Depression: A Propensity Score-Matched Cohort Study

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Background: Depression is one of the most disabling disorders, which causes long-term complications such as neurodegenerative disorder and cerebrovascular disease. Some patients with depression seek acupuncture treatment. We aimed to investigate the association between acupuncture treatment and the risk of dementia in patients with depression from the perspective of real-world evidence.

Methods: Patients over 18 years old and newly diagnosed with depression between 1997 and 2010 were selected from the Taiwanese National Health Insurance Research Database and followed up until the end of 2013. Propensity score was used to match equal numbers of patients 1:1 (N = 16,609 per group) into acupuncture and non-acupuncture cohorts based on characteristics including sex, age, baseline comorbidity and drug use. The outcome measurement was the comparison of dementia incidence in the two cohorts.

Results: Compared with the non-acupuncture cohort, patients who received acupuncture treatment had a decreased risk of dementia (adjusted hazard ratio (aHR) = 0.54; 95% confidence interval (CI) = 0.50–0.58, P < 0.001) after adjustment for age, sex, comorbidities and drug use. Compared with depression patients who did not receive acupuncture, the aHR of vascular dementia and Alzheimer’s disease incidences for patients who had acupuncture therapy was 0.59 (95% CI 0.48–0.71) and 0.51 (95% CI 0.39–0.67), respectively. The cumulative incidence of dementia was significantly lower in the acupuncture cohort than in the non-acupuncture cohort (Log rank test, p < 0.001).

Conclusion: The present study from real-world data revealed that acupuncture reduced the risk of dementia in depression patients, which supports healthcare decisions in clinical practice.

Keywords: acupuncture, Alzheimer’s disease, depression, dementia, National Health Insurance Research Database, NHIRD, traditional Chinese medicine

Introduction
Depression, also called major depressive disorder (MDD), is a condition characterized by a gloomy (depressed) mood or anhedonia, which means a loss of interest in usually pleasurable activities. The DSM-5 criteria for major depressive disorder (MDD) include the presence of either of those symptoms for at least two weeks, plus four or more following symptoms: low energy or fatigue, insomnia or hyper-somnia, loss or increased appetite/weight, psychomotor retardation or agitation, poor concentration or indecisiveness, suicidal ideation, and pathological guilt or
feelings of worthlessness. Depression is common among adults worldwide. The World Health Organization estimates that 350 million people globally have depressive episodes. The World Mental Health Survey conducted in 17 countries found that, on average, approximately 5% of people have had depressive episodes. Moreover, approximately 1 million people with depression lose their lives due to suicide yearly, which means 3000 suicide deaths per day.3

Dementia is one of the major causes of disability in old age. It is a condition that is characterized by a decrease in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor function, social cognition)2,4 As of 2010, there were 35.6 million people with dementia worldwide. The number is predicted to reach 65.7 million in 2030 and 115.4 million in 2050.5 Dementia mainly affects older people, and its prevalence increases exponentially with age. Depression and dementia commonly occur together in elderly people. Recent studies indicate that early-life depression could be a risk factor for later dementia and that later-life depression is a prodrome of dementia.6 These findings show the importance of effective treatment for depression, which may reduce the prevalence of dementia.

The most common standard initial therapy for depression consists of psychotherapy and antidepressants such as SSRIs, MAOIs, TCAs, SNRIs, NDRIs, SARIs and NaSSAs.7 However, antidepressants may cause side effects such as weight gain, sedation, dry mouth, nausea, blurred vision, constipation, and tachycardia.8,9 Therefore, some patients who suffer from depression may seek complementary or alternative treatments. One American survey revealed that 34% of psychiatric outpatient patients with depression were using alternative therapies.10 Another survey showed that 20% of depressed Americans had used complementary and alternative medicine therapy, including acupuncture, for their depression.11 In addition, among people seeking acupuncture in the United Kingdom, psychological distress, including depression, was the second most common reason.12 Acupuncture is one of the most popular complementary therapies in Taiwan.13,14 Some previous studies have indicated the benefits of acupuncture for depression. Chan’s systematic review and meta-analysis indicated that acupuncture combined with antidepressants is effective against depression. The therapeutic efficacy of the combination was better than that of antidepressants alone.15 Similar results were also found in another systematic review and meta-analysis, which indicated that early treatment of primary depression using SSRIs combined with electroacupuncture therapy was more efficient than SSRIs alone and led to better and earlier control of depressive symptoms.16 Another systematic review and meta-analysis showed that the incidence of side effects of acupuncture intervention was significantly lower than that of antidepressants in depression patients.17 Recent research shows that acupuncture may also be safe for treating dementia and may enhance the positive effect of drugs on cognitive function, allowing dementia patients to go about their daily lives.18 However, none of them have shown the evidence regarding the effects of acupuncture on the progression to dementia in patients with depression.

Taiwan launched the National Health Insurance (NHI) program in 1995. This compulsory insurance program covers more than 99% of all residents in Taiwan, and it provides universal care to the people of Taiwan. The NHI program began reimbursing Western medical services in 1995 and traditional Chinese medicine (TCM) services in 1996. The NHI administration has established a National Health Insurance Research Database (NHIRD), which includes all claims data. These datasets provided real-world data with long-term follow-up information, reducing the potential for sampling bias.19 Our previous studies have also shown that acupuncture treatment is beneficial for patients with fibromyalgia,20,21 arthritis,22,23 and depression24 in the NHIRD. As recently noted, “real-world” data are not inferior to clinical trials and may provide useful information.25 Due to the shortage of existing long-term follow-up studies, our study aims to determine whether acupuncture can decrease the risk of progression to dementia in patients with depression by using a random sample of one million patients selected from the NHIRD.

Materials and Methods
Data Source
The data in this study are selected from the Taiwanese NHIRD (https://nhird.nhri.org.tw/en/), which contains the registration files and original claims data for reimbursements, including demographic characteristics, diagnoses, clinical visits, hospitalizations, procedures, prescriptions, and the medical costs for reimbursement; this information is provided to scientists in Taiwan for research purposes.
The NHI program covers TCM services, including Chinese herbal medicine, manipulative therapies and acupuncture. The diagnostic codes follow the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

**Study Population and Variables**
The flowchart for enrolling patients with depression and dementia is shown in Figure 1. A sample of one million randomly selected individuals from the NHIRD database was used in this study. Patients (n = 65,569) with diagnosed depression (ICD-9-CM code: 296.2–296.3, 300.4, 311) between January 1997 and December 2010 were included in this study and then followed up until the end of 2013. Next, we narrowed the selection to patients who were newly diagnosed with depression between 1997 and 2010 and had at least 2 claims during that period. We excluded 1840 individuals who were younger than 18 years of age or who had missing information such as date of birth or sex. In addition, we excluded 3343 individuals whose date of dementia diagnosis (ICD-9-CM: 290, 294.1, 331.0–331.2) was before the date of depression diagnosis. In all, after these exclusions, there were 49,993 patients with newly diagnosed depression and at least 2 claims during the period from 1997 to 2010. The remaining patients were divided into two groups: those who received acupuncture treatment (n = 23,149) and those

![Flow chart of the selection of patients with depression from the National Health Insurance Research Database (NHIRD) between 1997 and 2000 in Taiwan. After excluding the patients who did not meet the inclusion criteria and matching by propensity score, the acupuncture and non-acupuncture cohorts each contained an equal number of patients.](image-url)
who did not (n=26,844). We defined the date of first acupuncture treatment after the date of the new depression diagnosis as the index date for the acupuncture group, and we randomly chose a date between the date of the new depression diagnosis and the endpoint as the index date for the control group. The acupuncture treatment (n =16,609) group and the control (n=16,609) group were matched 1:1 for propensity score by age (in 5-year bins), sex, index year, initial year of diagnosis of depression, all comorbidities, and all drugs used (oral steroids; nonsteroidal anti-inflammatory drugs (NSAIDs); statins; and selective serotonin reuptake inhibitors (SSRIs: escitalopram, fluvoxamine, sertraline), monoamine oxidase inhibitors (MAOIs: selegiline, isocarboxazid, tranylcypromine, phenelzine, moclobemide), tricyclic antidepressants (TCAs: amoxapine, desipramine, imipramine, doxepin, clomipramine, trimipramine) and other antidepressant drugs (serotonin–norepinephrine reuptake inhibitors, SNRIs: venlafaxine, duloxetine, milnacipran; norepinephrine–dopamine reuptake inhibitor, NDRI: bupropion; serotonin antagonist and reuptake inhibitor, SARI: mescaline; noradrenergic and specific serotonergic antidepressant, NaSSA: mirtazapine)) (Figure 1).

**Ethical Considerations**

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The National Health Research Institutes encrypted all information that could be used to identify individuals or care providers before release; it is therefore impossible to identify any individuals or care providers in the database. The Research Ethics Committee of China Medical University and Hospital approved this study and waived the requirement for informed consent (CMUH104-REC2-115).

**Availability of Data and Material**

The datasets analyzed from NHIRD were provided by the National Health Insurance Administration and maintained by the National Health Research Institutes of Taiwan. The use of NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p=987) and related regulations of the National Health Insurance Administration and National Health Research Institutes.

**Statistical Analysis**

We used SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), to analyze the data from the NHIRD. Descriptive statistics were applied to determine the demographic characteristics, treatment modalities, and frequency of prescriptions for acupuncture. The diagnoses were coded according to the ICD-9-CM codes. Data missing the important information such as date of birth or sex were excluded. To present the overall structure of the study groups, we calculated the mean and standard deviation (SD) for age and the percentage for sex, comorbidity, drug use, and types of acupuncture. To evaluate the distribution differences between acupuncture and non-acupuncture users, we used Student’s t-test for continuous variables and the chi-squared test for categorical variables. The Cox proportional hazard regression model was applied to estimate the hazard ratio (HR) and 95% confidence interval (CI) of dementia in patients with depression who received acupuncture compared with non-acupuncture users. We also used the Kaplan-Meier method and the Log rank test to estimate the cumulative risk of dementia with depression between acupuncture users and non-acupuncture users.

**Results**

After propensity score-matching by age (per 5 years), sex, index year, initial year of diagnosis of depression, all comorbidities, and drugs used (oral steroids; NSAIDs; statins; and SSRIs, MAOIs, TCAs and other antidepressant drugs), the acupuncture users (n=16,609) and non-acupuncture users (n=16,609) had similar demographic characteristics. Most acupuncture users received manual acupuncture (87.14%), while some received electroacupuncture (2.97%) and others used a combination of manual acupuncture and electroacupuncture (9.89%) (Table 1).

Compared with depression patients who did not receive acupuncture treatment, the adjusted hazard ratio for dementia in patients who received acupuncture therapy was 0.54 (95% CI, 0.50–0.58, P < 0.001) (Table 2). The age-stratified results demonstrated that the risk of dementia increased with age. Depression patients over 60 years old had the highest risk of dementia (aHR, 26.51; 95% CI, (21.39–32.86), P < 0.001). Regarding comorbidities before the initial diagnosis date of depression, there was no significant relationship between the risk of dementia and anxiety, tobacco use or obesity. However, there was a significant relationship between the risk of dementia and comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and alcoholism. Depression patients with these comorbidities had an elevated risk of dementia (Table 2).
In addition, there was a significant relationship between the risk of dementia and whether drugs were used to treat depression after diagnosis. Compared to the group who did not use drugs, the patients who used SSRIs, MAOIs and TCAs had an elevated aHR (1.09, 1.47 and 1.1). This may be because patients who used these anti-depressants initially had more severe depression than those who did not take them. However, the patients who used oral steroids, NSAIDs, statins and other antidepressant drugs had reduced aHRs (0.53, 0.20, 0.56 and 0.71).

In this study, 1071 patients in the acupuncture cohort (12.11 per 1000 person-years) and 1436 patients in the non-acupuncture cohort (19.68 per 1000 person-years) developed dementia (Table 3). The beneficial effect of acupuncture on the incidence of dementia was noted in both female and male patients (female aHR, 0.53; 95% CI, 0.48–0.58; male aHR, 0.56; 95% CI, 0.49–0.63). Although the risk of dementia gradually increased with age, acupuncture significantly decreased the progression of dementia in all age groups. Acupuncture decreased the risk of

| Table 1 Characteristics of Depression Patients According to Whether They Received Acupuncture |
| Variable | Accepted Acupuncture | p-value* |
|----------|----------------------|----------|
|          | No (n =16,609)       | Yes (n =16,609) |
|          | n           | %       | n           | %       |
| Sex      |             |         |             |         | 0.9188  |
| Women    | 10,349      | 62.31%  | 10,358      | 62.36%  |
| Men      | 6260        | 37.69%  | 6251        | 37.64%  |
| Age group|           |         |             |         | 0.99    |
| 18–39    | 6520        | 39.26%  | 6520        | 39.26%  |
| 40–59    | 7693        | 46.32%  | 7693        | 46.32%  |
| ≥60      | 2396        | 14.34%  | 2396        | 14.34%  |
| Baseline comorbidity |         |         |             |         | 0.9746  |
| Diabetes mellitus | 2613    | 15.73%  | 2714        | 16.34%  | 0.131   |
| Hypertension  | 5125    | 30.86%  | 5125        | 30.86%  | 0.99    |
| Hyperlipidemia | 4076    | 24.54%  | 3993        | 24.04%  | 0.2883  |
| Congestive heart failure | 413     | 2.49%   | 413         | 2.49%   | 0.99    |
| Anxiety    | 166       | 1.01%   | 168         | 1.01%   | 0.9124  |
| Alcoholism | 296      | 1.78%   | 284         | 1.71%   | 0.6152  |
| Tobacco use | 132     | 0.79%   | 130         | 0.78%   | 0.9013  |
| Obesity    | 160       | 0.96%   | 148         | 0.89%   | 0.4921  |
| Drugs used |          |         |             |         | 0.99    |
| Oral steroids | 13,069 | 78.69%  | 13,052      | 78.58%  | 0.82    |
| NSAIDs    | 16,490     | 99.28%  | 16,497      | 99.33%  | 0.644   |
| Statins   | 4144       | 24.95%  | 4144        | 24.95%  | 0.99    |
| SSRIs     | 10,354     | 62.34%  | 10,317      | 62.12%  | 0.6754  |
| MAOIs     | 1341       | 8.07%   | 1349        | 8.12%   | 0.8722  |
| TCAs      | 6225       | 37.48%  | 6225        | 37.48%  | 0.99    |
| Other antidepressant drugs | 5512 | 33.19%  | 5496        | 33.09%  | 0.8521  |
| Types of acupuncture |         |         |             |         | 0.99    |
| Manual acupuncture | –       | –       | 14,473      | 87.14%  |
| Electroacupuncture | –      | –       | 494         | 2.97%   |
| Combination of manual acupuncture and electroacupuncture | – | – | 1642 | 9.89% |
| Duration between depression date and index date, days (mean, median) | 1405.73(1115) | 1398.74(1077) |

Notes: *Chi-squared test; †t-test.
dementia in patients with depression with and without comorbidities (diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, anxiety, alcoholism, tobacco use, and obesity). Regardless of whether patients took oral steroids; NSAIDs; statins; or SSRIs, MAOIs, TCAs and other antidepressant drugs, fewer patients in the acupuncture cohort than in the non-acupuncture cohort developed dementia.

We also analyzed the incidence rates, hazard ratio and confidence intervals of vascular dementia (ICD-9-CM: 290.4) and Alzheimer’s disease (ICD-9-CM: 331.0) for depression patients who received acupuncture and those who did not. The acupuncture cohort had a reduced risk of vascular dementia and Alzheimer’s disease (Table 4). In this study, 193 patients in the acupuncture cohort (2.18 per 1000 person-years) and 226 patients in the non-acupuncture cohort (3.19 per 1000 person-years) developed vascular dementia. Compared with depression patients who did not receive acupuncture, the aHR of vascular dementia incidence for patients who had acupuncture therapy was 0.59 (95% CI 0.48–0.71). There were 96 patients in the acupuncture cohort (1.08 per 1000 person-years) and 126 patients in the non-acupuncture cohort (1.72 per 1000 person-years) who developed Alzheimer’s disease. Compared with depression patients who did not receive acupuncture, the aHR of

| Variable | No. of Events (n=2507) | Crude* | Adjusted† |
|----------|------------------------|--------|-----------|
|          | HR (95% CI)            | p-value| HR (95% CI) | p-value |
| Received acupuncture | No | 1436 | 1.00 | Reference | 1.00 | Reference |
|          | Yes | 1071 | 0.63 | (0.58–0.68) | <0.0001 | 0.54 | (0.50–0.58) | <0.0001 |
| Sex | Women | 1557 | 1.00 | Reference | 1.00 | Reference |
|          | Men | 950 | 0.97 | (0.89–1.05) | 0.4437 | 0.98 | (0.92–1.06) | 0.5538 |
| Age group | 18–39 | 106 | 1.00 | Reference | 1.00 | Reference |
|          | 40–59 | 959 | 7.38 | (6.04–9.02) | <0.0001 | 6.24 | (5.08–7.67) | <0.0001 |
|          | ≥60 | 1442 | 41.87 | (34.37–51) | <0.0001 | 26.51 | (21.39–32.86) | <0.0001 |
| Baseline comorbidity (ref=no comorbidity) | Diabetes mellitus | 902 | 3.14 | (2.9–3.41) | <0.0001 | 1.39 | (1.27–1.52) | <0.0001 |
|          | Hypertension | 1746 | 5.43 | (4.99–5.91) | <0.0001 | 1.86 | (1.68–2.05) | <0.0001 |
|          | Hyperlipidemia | 1142 | 2.84 | (2.63–3.08) | <0.0001 | 1.30 | (1.19–1.42) | <0.0001 |
|          | Congestive heart failure | 190 | 4.02 | (3.47–4.66) | <0.0001 | 1.19 | (1.02–1.39) | 0.0254 |
|          | Anxiety | 53 | 2.34 | (1.79–3.08) | <0.0001 | 1.04 | (0.79–1.37) | 0.7531 |
|          | Alcoholism | 26 | 0.65 | (0.44–0.96) | 0.0294 | 1.51 | (1.02–2.22) | 0.04 |
|          | Tobacco use | 9 | 0.65 | (0.34–1.25) | 0.0294 | 0.82 | (0.42–1.58) | 0.5512 |
|          | Obesity | 12 | 0.62 | (0.35–1.1) | 0.0294 | 0.65 | (0.37–1.14) | 0.1337 |
| Drugs used | Oral steroids | 1887 | 0.72 | (0.65–0.78) | <0.0001 | 0.53 | (0.48–0.63) | <0.0001 |
|          | NSAIDs | 2452 | 0.17 | (0.13–0.22) | <0.0001 | 0.2 | (0.15–0.27) | <0.0001 |
|          | Statins | 812 | 1.32 | (1.21–1.43) | <0.0001 | 0.56 | (0.51–0.61) | <0.0001 |
|          | SSRIs | 1398 | 0.79 | (0.73–0.85) | <0.0001 | 1.09 | (1.01–1.18) | 0.0354 |
|          | MAOIs | 360 | 1.65 | (1.48–1.85) | <0.0001 | 1.47 | (1.32–1.65) | <0.0001 |
|          | TCAs | 1291 | 1.61 | (1.49–1.74) | <0.0001 | 1.1 | (1.01–1.19) | 0.0227 |
|          | Other antidepressant drugs | 531 | 0.57 | (0.51–0.62) | <0.0001 | 0.71 | (0.64–0.78) | <0.0001 |

Notes: Crude HR* represents relative hazard ratio. Adjusted HR† represents adjusted hazard ratio: adjusted for acupuncture; age; sex; diabetes mellitus; hypertension; hyperlipidemia; congestive heart failure; anxiety; alcoholism; tobacco use; obesity; oral steroids; NSAIDs; statins; and SSRIs, MAOIs, TCAs and other antidepressant drugs in Cox proportional hazards regression.
Table 3 Incidence Rates, Hazard Ratios and Confidence Intervals of Dementia for Those Depression Patients Who Received Acupuncture and Those Who Did Not, Stratified by Sex, Age, Comorbidities and Drug Use

| Variables                        | Accepted Acupuncture | Compared with Non-Acupuncture Users |
|----------------------------------|----------------------|-------------------------------------|
|                                  | (n=16,609)           | (n=16,609)                          |
|                                  | Event Person-Years   | IR                    | Event Person-Years | IR | (95% CI) | (95% CI) |
| Total                            | 1436 72,967 19.68    | 1071 88,451 12.11      | Crude HR           | Adjusted HR† |
|                                  |                      |                      |                     |     | 0.63(0.58–0.68)*** | 0.54(0.50–0.58)*** |
| Sex                              |                      |                      |                     |     | 0.6(0.54–0.67)*** | 0.53(0.48–0.58)*** |
| Women                            | 907 44,834 20.23     | 650 53,965 12.04      |                     |     | 0.67(0.59–0.76)*** | 0.56(0.49–0.63)*** |
| Men                              | 529 28,133 18.80     | 421 34,485 12.21      |                     |     | 0.54(0.50–0.58)*** | 0.56(0.51–0.63)*** |
| Age group                        |                      |                      |                     |     |                |            |
| 18–39                            | 84 29,388 2.14       | 43 33,886 1.27        | 0.61(0.41–0.9)*     | 0.6(0.41–0.88)** |
| 40–59                            | 593 35,517 16.70     | 366 42,337 8.64       | 0.52(0.46–0.6)**    | 0.5(0.44–0.57)** |
| ≥60                              | 780 80,62 96.76      | 662 12,228 54.14      | 0.58(0.52–0.65)***  | 0.56(0.51–0.63)*** |
| Baseline comorbidity             |                      |                      |                     |     |                |            |
| Diabetes mellitus                |                      |                      |                     |     |                |            |
| No                               | 947 62,974 15.04     | 658 74,125 8.88       | 0.6(0.54–0.66)***   | 0.54(0.49–0.59)*** |
| Yes                              | 489 9992 48.94       | 413 14,326 28.83      | 0.61(0.53–0.69)***  | 0.54(0.48–0.62)*** |
| Hypertension                     |                      |                      |                     |     |                |            |
| No                               | 446 52,435 8.51      | 315 61,220 5.15       | 0.61(0.53–0.71)***  | 0.55(0.48–0.64)*** |
| Yes                              | 990 20,532 48.22     | 756 27,230 27.76      | 0.59(0.54–0.65)***  | 0.53(0.48–0.58)*** |
| Hyperlipidemia                   |                      |                      |                     |     |                |            |
| No                               | 783 56,817 13.78     | 582 68,164 8.54       | 0.6(0.56–0.7)**     | 0.54(0.49–0.6)*** |
| Yes                              | 653 16,150 40.43     | 489 20,286 24.10      | 0.61(0.54–0.69)***  | 0.54(0.48–0.6)*** |
| Congestive heart failure         |                      |                      |                     |     |                |            |
| No                               | 1336 71,659 18.64    | 981 86,606 11.33      | 0.62(0.57–0.67)***  | 0.54(0.49–0.58)*** |
| Yes                              | 100 1308 76.48       | 90 1845 48.78        | 0.65(0.49–0.86)**   | 0.54(0.4–0.73)*** |
| Anxiety                          |                      |                      |                     |     |                |            |
| No                               | 1406 72,367 19.43    | 1048 87,591 11.96     | 0.63(0.58–0.68)***  | 0.54(0.5–0.59)*** |
| Yes                              | 30 599 50.06         | 23 859 26.77         | 0.55(0.32–0.95)*    | 0.46(0.26–0.81)** |
| Alcoholism                       |                      |                      |                     |     |                |            |
| No                               | 1419 71,892 19.74    | 1062 86,990 12.21     | 0.63(0.58–0.68)***  | 0.54(0.5–0.59)*** |
| Yes                              | 17 1075 15.82        | 9 1461 6.16        | 0.41(0.18–0.93)*    | 0.36(0.15–0.86)* |
| Tobacco use                      |                      |                      |                     |     |                |            |
| No                               | 1430 72,565 19.71    | 1068 88,016 12.13     | 0.63(0.58–0.68)***  | 0.54(0.5–0.58)*** |
| Yes                              | 6 402 14.92          | 3 435 6.90          | 0.46(0.11–1.84)     | 0.65(0.12–3.43) |
| Obesity                          |                      |                      |                     |     |                |            |
| No                               | 1427 72,446 19.70    | 1068 87,761 12.17     | 0.63(0.58–0.68)***  | 0.54(0.5–0.59)*** |
| Yes                              | 9 520 17.30          | 3 690 4.35          | 0.25(0.07–0.93)*    | 0.16(0.03–0.8)* |
| Drugs used                       |                      |                      |                     |     |                |            |
| Oral steroids                    |                      |                      |                     |     |                |            |
| No                               | 390 13,866 28.13     | 230 16,465 13.97     | 0.52(0.44–0.61)***  | 0.48(0.41–0.57)*** |
| Yes                              | 1046 59,101 17.70    | 841 71,985 11.68     | 0.66(0.6–0.72)***   | 0.56(0.51–0.62)*** |

(Continued)
Table 3 (Continued).

| Variables | Accepted Acupuncture | Compared with Non-Acupuncture Users |
|-----------|----------------------|-------------------------------------|
|           | No (n=16,609) | Yes (n=16,609) | Crude HR | Adjusted HR† |
|           | Event | Person-Years | IR | Event | Person-Years | IR | (95% CI) | (95% CI) |
| NSAIDs    | No | 36 | 211 | 170.31 | 19 | 362 | 52.56 | 0.41(0.23–0.71)*** | 0.32(0.16–0.63)*** |
|           | Yes | 1400 | 72,755 | 19.24 | 1052 | 88,089 | 11.94 | 0.63(0.58–0.68)*** | 0.55(0.5–0.59)*** |
| Statins   | No | 983 | 53,146 | 18.50 | 712 | 64,936 | 10.96 | 0.61(0.55–0.67)*** | 0.51(0.46–0.56)*** |
|           | Yes | 453 | 19,821 | 22.85 | 359 | 23,514 | 15.27 | 0.67(0.57-0.77)*** | 0.61(0.53–0.7)*** |
| SSRLs     | No | 633 | 27,835 | 22.74 | 476 | 34,189 | 13.83 | 0.63(0.56–0.71)*** | 0.54(0.48–0.61)*** |
|           | Yes | 803 | 45,132 | 17.79 | 595 | 54,032 | 11.01 | 0.62(0.56–0.69)*** | 0.53(0.48–0.59)*** |
| MAOIs     | No | 1228 | 66,420 | 18.49 | 919 | 79,906 | 11.50 | 0.63(0.58–0.69)*** | 0.54(0.5–0.59)*** |
|           | Yes | 208 | 6546 | 31.77 | 152 | 8544 | 17.79 | 0.58(0.47–0.71)*** | 0.52(0.42–0.64)*** |
| TCAs      | No | 714 | 44,222 | 16.15 | 502 | 52,576 | 9.55 | 0.61(0.54–0.68)*** | 0.51(0.45–0.57)*** |
|           | Yes | 722 | 28,745 | 25.12 | 569 | 35,875 | 15.86 | 0.64(0.57–0.71)*** | 0.57(0.51–0.63)*** |
| Other antidepressant drugs | No | 1147 | 49,042 | 23.39 | 829 | 60,722 | 13.65 | 0.60(0.55–0.66)*** | 0.53(0.48–0.58)*** |
|           | Yes | 289 | 23,925 | 12.08 | 242 | 27,728 | 8.73 | 0.71(0.6–0.85)*** | 0.57(0.47–0.67)*** |

Notes: Adjusted HR†: adjusted for acupuncture; age; sex; diabetes mellitus; hypertension; hyperlipidemia; congestive heart failure; anxiety; alcoholism; tobacco use; obesity; oral steroids; NSAIDs; statins; and SSRLs, 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 1000 person-years); HR, hazard ratio; CI, confidence interval.

Alzheimer’s disease incidence for patients who had acupuncture therapy was 0.51 (95% CI 0.39–0.67).

Figure 2 reveals the cumulative incidence of dementia. Overall, the results suggest that in patients with depression, the cumulative incidence of dementia was lower in acupuncture users than in non-acupuncture users during the follow-up period (Log rank test, P < 0.001).

Table 4 Incidence Rates, Hazard Ratio and Confidence Intervals of Vascular Dementia (ICD-9-CM: 290.4) and Alzheimer’s Disease (ICD-9-CM: 331.0) for Those Depression Patients Who Received Acupuncture and Those Who Did Not, Stratified by Sex, Age, Comorbidities and Drug Use

| Variables          | Acupuncture | Compared with Non-Acupuncture Users |
|--------------------|-------------|-------------------------------------|
|                    | No (n=16,933) | Yes (n=16,933) | Crude HR | Adjusted HR† |
|                    | Event | Person-Years | IR | Event | Person-Years | IR | (95% CI) | (95% CI) |
| Vascular dementia  | 226 | 73,247 | 3.09 | 193 | 88,612 | 2.18 | 0.70(0.57–0.84)*** | 0.59(0.48–0.71)*** |
| Alzheimer’s disease| 126 | 73,210 | 1.72 | 96 | 88,559 | 1.08 | 0.61(0.47–0.80)*** | 0.51(0.39–0.67)*** |

Notes: Adjusted HR†: adjusted for acupuncture; age; sex; diabetes mellitus; hypertension; hyperlipidemia; congestive heart failure; anxiety; alcoholism; tobacco use; obesity; oral steroids; NSAIDs; statins; and SSRLs, MAOIs, TCAs and other antidepressant drugs in Cox proportional hazards regression. ***p<0.001.

Abbreviations: IR, incidence rate (per 1000 person-years); HR, hazard ratio; CI, confidence interval.
In this study, we provided some evidence, although not a clinical trial, from the “real-world” data demonstrating the association between the acupuncture treatments and the reduced risk of developing dementia in patients with depression. Our study has several strengths. The “real-world” data from the NHIRD provided large-scale cohort with long-term follow-up data.

The current knowledge regarding the efficacy of clinical intervention is usually limited to clinical trials. None of the previous data regarding the utilization of acupuncture for depression are supported by large-scale “real-world” data. As all patients with depression were registered in the NHI program since 1995, we were able to use the database to perform this study. These datasets provide a nationwide population-based claim database with long-term follow-up data. Thus, this propensity-score matched data are highly reliable, reducing the potential for sampling and allocation bias.

As a popular alternative treatment for depression, acupuncture has been performed on patients with depression in several clinical trials. However, most previous studies have focused on the effectiveness and safety of acupuncture therapy in depressive disorders. In addition, current studies on the benefits of acupuncture for depression and dementia are limited. Systematic reviews have shown the disadvantages of recent clinical trials, such as small sample size, uncertain description of enrolment criteria, poor quality of randomization or blinding, and different forms of acupuncture. Our research showed that depression patients who received acupuncture had a lower risk of developing dementia than the non-acupuncture cohort. To the best of our knowledge, this is the first large-scale population-based cohort study to demonstrate a decreased dementia risk in depression patients receiving acupuncture therapy.

Acupuncture may be associated with a reduced risk of dementia in patients with depression for several reasons. Recent studies have presented some possible explanations for the benefits of acupuncture against dementia. In a series of studies using animal models of Alzheimer’s disease, electroacupuncture stimulation reduced mitochondrial damage and amyloid beta plaques in the hippocampal CA1 region and increased the levels of choline acetyltransferase (ChAT) in the brain, as well as the capacity for learning and memory. A previous mouse study found that acupuncture completely or partially reversed some aging-related changes in hippocampal gene expression profiles. Other mouse research also showed that acupuncture reduced cognitive deficits and neuronal loss in the hippocampal CA3 region and DG. In addition, a previous research indicated that electroacupuncture decreased Aβ protein expression and oxidative damage in the hippocampus of a rat model. Stem cell mobilization and progenitor cell proliferation in the central nervous system may also occur after acupuncture treatment for neurodegenerative diseases.

A previous study using resting-state functional magnetic resonance imaging (RS-fMRI) found that acupuncture stimulation could modulate the activity of the default mode network in Alzheimer’s disease patients. Another fMRI study indicated that acupuncture could improve hippocampal connectivity in Alzheimer’s disease patients. It was also found that the right hemisphere (the temporal lobe, such as the hippocampal gyrus; the insula; and some areas of the parietal lobe) and left hemisphere (the temporal lobe, the parietal lobules, and some regions of the cerebellum) were activated after acupuncture therapy. The regions activated by acupuncture overlap with the areas of the brain that are impaired in Alzheimer’s disease patients.

Alzheimer’s disease is the most common form of dementia in the elderly, accounting for 60–80% of cases. After Alzheimer’s disease, vascular dementia is
the second most common form of dementia in most clinical series, accounting for 10–20% of cases in North America and Europe. In this study, we found that the acupuncture cohort with depression had a lower risk of vascular dementia and Alzheimer’s disease compared with depression patients who did not receive acupuncture. The common mechanism that acupuncture reduced the risk of both types of dementia still need further laboratory investigations.

It has to be point out that our research also has some limitations. First, the NHIRD did not provide data to measure the severity of depressive disorders. To minimize this confounding factor, we performed 1:1 propensity score matching to ensure that all the baseline characteristics of both cohorts (including the anti-depressants) were similar. Second, the lifestyles of the two cohorts could be different. The NHIRD did not provide data about patients’ lifestyles, such as smoking frequency, body mass index (BMI), stress, and exercise. Studies have indicated that many dementia cases are attributable to risk factors such as obesity, physical inactivity, and smoking. Since data on lifestyle factors were deficient, we had only a limited ability to study these personal habits and customs in connection with illness. We performed 1:1 propensity score matching including the diagnoses of tobacco use and obesity and found that the comorbidities of both cohorts were similar. However, the percentages of smoking and obesity were still underestimated in both cohorts. Third, patients who seek acupuncture may have an increased level of motivation to address depression. Although the co-pay of acupuncture therapy is low (5–7 USD per treatment) under the NHI program, it is still a burden for poor people to consult doctors frequently. Thus, acupuncture users may have greater financial ability to obtain tangible or intangible resources than non-users.

**Conclusion**

Patients who suffer from depression may utilize complementary therapies; in Taiwan, many patients choose acupuncture. Our study suggests that acupuncture treatment is associated with a reduced risk of dementia in patients with depression. We hope that additional clinical trials and research studies based on this study’s findings will be undertaken in the future. Further research is necessary to determine the mechanism behind the protective effect of acupuncture.

**Data Sharing Statement**

The datasets we used in this study were released by the Taiwan NHIRD (https://nhird.nhri.org.tw/en/), maintained and managed by National Health Research Institutes, 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 substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. Mei-Yao Wu and Hung-Rong Yen contributed equally as co-corresponding authors.

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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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