




BMJ Open Effect of acupuncture on ischaemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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ABSTRACT

Objective To demonstrate that acupuncture is beneficial for decreasing the risk of ischaemic stroke in patients with rheumatoid arthritis (RA).

Design A propensity score-matched cohort study.

Setting A nationwide population-based study.

Participants Patients with RA diagnosed between 1 January 1997 and 31 December 2010, through the National Health Insurance Research Database in Taiwan.

Interventions Patients who were administered acupuncture therapy from the initial date of RA diagnosis to 31 December 2010 were included in the acupuncture cohort. Patients who did not receive acupuncture treatment during the same time interval constituted the no-acupuncture cohort.

Primary outcome measures A Cox regression model was used to adjust for age, sex, comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of ischaemic stroke between these two cohorts through competing-risks regression models.

Results After 1:1 propensity score matching, a total of 23 226 patients with newly diagnosed RA were equally subgrouped into acupuncture cohort or no-acupuncture cohort according to their use of acupuncture. The basic characteristics of these patients were similar. A lower cumulative incidence of ischaemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$; immortal time (period from initial diagnosis of RA to index date) 1065 days; mean number of acupuncture visits 9.83. In the end, 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1000 person-years) experienced ischaemic stroke (adjusted SHR 0.57, 95% CI 0.50 to 0.65). The advantage of lowering ischaemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

Conclusions This study showed the beneficial effect of acupuncture in reducing the incidence of ischaemic stroke in patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a common rheumatoid disease that manifests as polyarthritis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Our research discloses the possible long-term effect of acupuncture on stroke prevention that could not be investigated in clinical trials.
- ⇒ Lower incidence of ischaemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.
- ⇒ The causality could not be proven directly through our study design.

in the joints, mainly synovial inflammation and morning stiffness.¹ Bone erosion, joint deformity, and loss of functional abilities are long-term complications of RA. In regard to chronic processes, the inflammation status can be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular disease.^{2–5} Comorbidities from cardiovascular disease, such as stroke, are the major cause of death in RA patients.^{6–11} Compared with the general population, stroke is more common in RA patients.¹² The prevalence of RA globally and in Asia is 460 per 100 000 people and 15.8 per 100 000 people, respectively.^{13–15} However, the risk of developing ischaemic stroke in Asian RA patients (hazard ratio (HR) 1.32) is similar to that in Caucasian populations (HR 1.29).^{16 17}

Determining the agents to prevent stroke is an essential issue for clinical doctors and patients.¹⁸ The common prescriptions to treat RA are non-steroidal anti-inflammatory drugs (NSAIDs), steroids, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF- α inhibitor), and anakinra (IL-1 inhibitor).^{3 5 19} Steroids and DMARDs, such as methotrexate and infliximab, have advantages in the prevention of ischaemic

stroke in RA patients.¹⁸ However, some of them could result in complications in the bone marrow that cause thrombocytopenia.²⁰ Finding alternative interventions to control RA while lowering complications from treatment itself has become a well-discussed topic.

In many countries, such as Taiwan, Germany, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA.^{21–25} A previous cohort study found that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) services, and 23.6% of these patients had received acupuncture.²⁶ Furthermore, secondary stroke prevention is also noted to result from acupuncture therapy in the Taiwanese population.²⁷ The hypothesised mechanism by which acupuncture lowers the stroke rate is similar to that of anti-RA agents—anti-inflammation. Thus, we wanted to investigate the relationship between acupuncture intervention and the incidence of ischaemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of the National Health Insurance (NHI) program—the National Health Insurance Research Database (NHIRD). This service of the NHI has been operating from 1995 until now, and the coverage rate in the Taiwanese population is more than 99%.²⁸ In other words, the medical data in the NHIRD cover a long enough time and are large enough to be used for nationwide population research. Sampling bias could be prevented when the study is conducted through such a large-scale database.²⁹ We used the NHIRD to investigate the long-term effect of ischaemic stroke prevention in patients with RA who accepted acupuncture treatment.

METHODS

Data sources

A nationwide, population-based 1:1 propensity score-matched cohort study via data analysis derived from the NHIRD was performed. The database used in this study was the Registry for Catastrophic Illness Patients Database (RCIPD), which is part of the NHIRD. Personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research. The RCIPD enrolled all patients with a catastrophic illness, which was proven by pathological, laboratory, and clinical diagnoses by both specialists and a regular review. This real-world database consists of datasets including demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, remedies, procedures, and medical expenses for reimbursement. The diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with a diagnosis of RA are issued catastrophic illness certificates and receive free medical services for health complications. Thus, the RCIPD is an ideal comprehensive database

for the investigation of all RA patients in Taiwan. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH109-REC2-031 (CR-3)).

Study subjects and variables

We used both ambulatory and inpatient medical records to identify RA treatments that were linked with the RCIPD from 1997 to 2010 to identify a study population (n=47 809) for follow-up until the end of 2011 (figure 1). Newly diagnosed RA patients (n=36 277) with a diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1793) as follows: (1) patients who were younger than 18 years; (2) patients who had incomplete data on age or sex; (3) patients who had an interruption in health insurance services during the follow-up period; and (4) patients who had a diagnosis of ischaemic stroke (ICD-9-CM: 433–438) before the index date. Finally, 23 226 newly diagnosed RA patients were included. Patients who received acupuncture therapy from the initial RA diagnosis to 31 December 2010 were included in the acupuncture cohort (n=12 266). We used a propensity score approach to minimise confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, types of drugs used (oral steroids, NSAIDs, statins, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. The definition of drugs used was patients with ≥28 cumulative use days. The numbers of participants in both the acupuncture and no-acupuncture cohorts were the same (n=11 613). The index date was defined as the first time that patients received acupuncture therapy, which was given randomly to patients in the no-acupuncture cohort according to the approach in the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Covariate assessment

The patients were assigned to three groups by age (18–39 years, 40–59 years, and ≥60 years). ICD-9-CM codes of comorbidities that appeared more than once in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM code 272), congestive heart failure (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), depression (ICD-9-CM 296.2–296.3, 300.4, 311), alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03, 790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), and atrial fibrillation (ICD-9-CM 427.3). The events of ischaemic stroke (ICD-9-CM: 433–438) were compared between the acupuncture and no-acupuncture cohorts of RA patients.

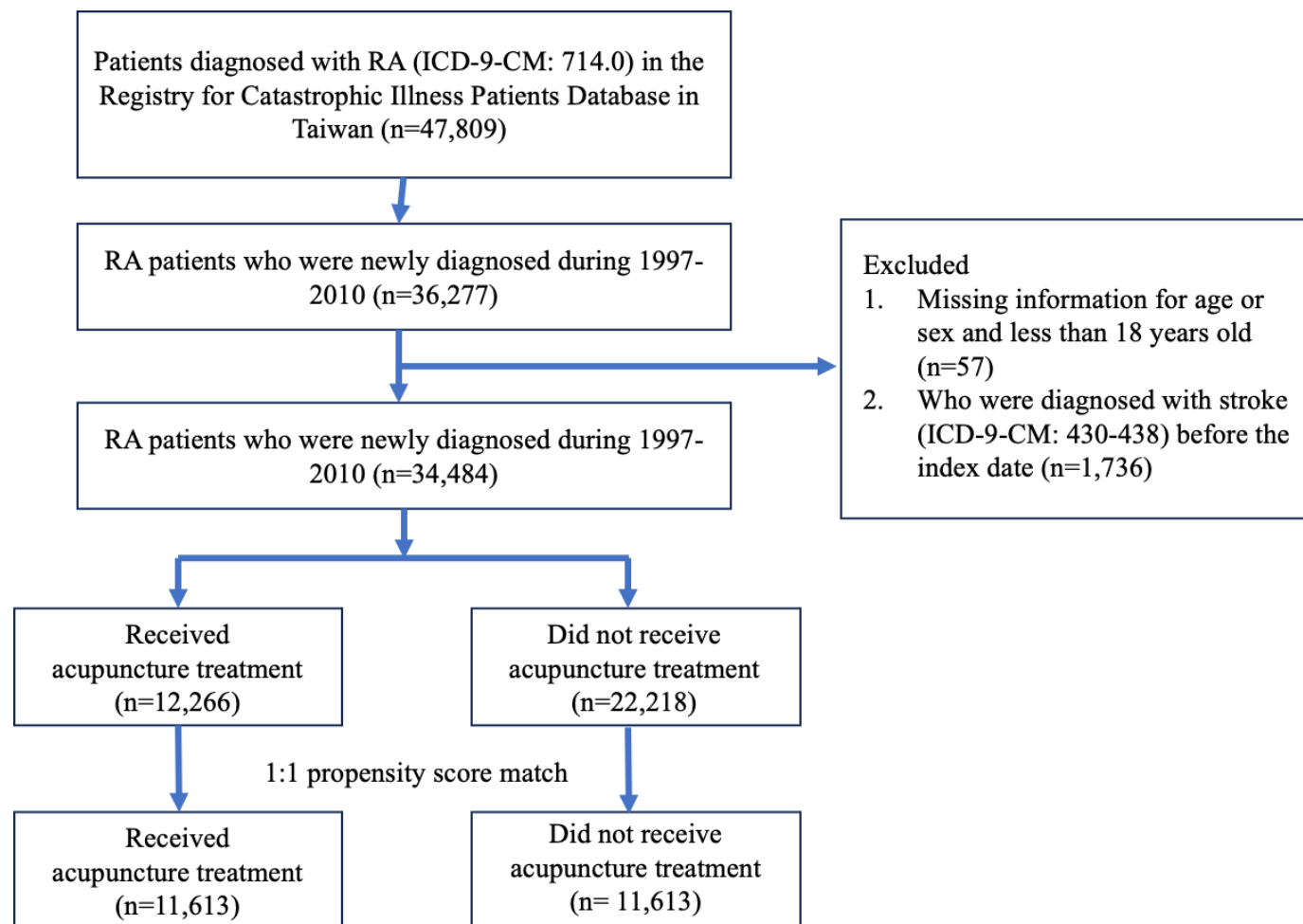


Figure 1 Study population flowchart. A total of 47 809 patients with RA were newly diagnosed from 1997 to 2010. Sex, age, comorbidities, types of drugs used, RA diagnosis year and index year were processed via 1:1 matching; subsequently, 11 613 patients were included in the acupuncture and no-acupuncture cohorts, respectively. RA, rheumatoid arthritis.

Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including manual acupuncture (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, and P32103) and electroacupuncture (B43, B44, B86, B87, B88, and B89), as previously described.³⁰

Statistical analyses

The standardised mean difference (SMD) was used to compare the baseline characteristics of the acupuncture and no-acupuncture cohorts as previously described.³⁰ A negligible difference in mean values or proportions between the two cohorts was defined as <0.1 SD. Competing-risk regression models were performed to estimate the crude and adjusted subhazard ratios (SHRs) of acupuncture therapy, age, sex, comorbidities, and types of drugs used. The Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischaemic stroke. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing,

Vienna, Austria) to perform statistical analyses and create the figures. Statistical significance was defined as $p < 0.05$ in two-tailed tests.

Patient and public involvement

None

RESULTS

We used 1:1 propensity score matching by sex, age, all comorbidities, drugs (oral steroids, NSAIDs, statins, all DMARDs), RA diagnosis year and index year to enrol an equal number ($n=11\,613$) of RA patients in the acupuncture cohort and no-acupuncture cohort, respectively (figure 1). The baseline characteristics of both cohorts are presented in table 1, with similar distributions of sex, age, comorbidities, and prescriptions. In both cohorts, most participants were female, and most patients were middle-aged (40–59 years). The most common comorbidity was hypertension; more than 38% of patients had this problem. In patients with RA, 18% had diabetes mellitus, 28% had hyperlipidaemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression.

Table 1 Characteristics of rheumatoid arthritis patients according to whether they received acupuncture treatment

| Variable | Rheumatoid arthritis | | | | Standardised mean difference |
|---|-----------------------|------|------------------|------|------------------------------|
| | Acupuncture treatment | | | | |
| | No (n=11 613) | | Yes (n=11 613) | | |
| | n | % | n | % | |
| Sex | | | | | |
| Women | 9499 | 81.8 | 9478 | 81.6 | 0.01 |
| Men | 2114 | 18.2 | 2135 | 18.4 | 0.01 |
| Age group (years) | | | | | |
| 18–39 | 1839 | 15.8 | 1588 | 13.7 | 0.06 |
| 40–59 | 6684 | 57.6 | 7330 | 63.1 | 0.11 |
| ≥60 | 3090 | 26.6 | 2695 | 23.2 | 0.08 |
| Mean±SD (years) | 54.9±14.5 | | 54.8±13.2 | | 0.01 |
| Baseline comorbidity | | | | | |
| Diabetes mellitus | 2176 | 18.7 | 2126 | 18.3 | 0.01 |
| Hypertension | 4507 | 38.8 | 4416 | 38.0 | 0.02 |
| Hyperlipidaemia | 3267 | 28.1 | 3273 | 28.2 | 0.001 |
| Congestive heart failure | 741 | 6.38 | 723 | 6.23 | 0.006 |
| Depression | 1256 | 10.8 | 1248 | 10.8 | 0.002 |
| Anxiety | 2880 | 24.8 | 2841 | 24.5 | 0.008 |
| Alcoholism | 208 | 1.79 | 221 | 1.90 | 0.008 |
| Tobacco use | 70 | 0.60 | 77 | 0.66 | 0.008 |
| Obesity | 130 | 1.12 | 135 | 1.16 | 0.004 |
| Atrial fibrillation | 741 | 6.38 | 715 | 6.16 | 0.009 |
| Drugs used | | | | | |
| Oral steroid | 6489 | 55.6 | 6495 | 55.9 | 0.001 |
| NSAID | 8823 | 76.0 | 8882 | 76.5 | 0.012 |
| Statin | 5592 | 5.10 | 593 | 5.11 | 0.000 |
| Conventional DMARDs | | | | | |
| Hydroxychloroquine | 5670 | 48.8 | 5663 | 48.8 | 0.001 |
| Sulfasalazine | 4295 | 37.0 | 4323 | 37.2 | 0.005 |
| Methotrexate | 9 | 0.08 | 10 | 0.09 | 0.003 |
| Leflunomide | 867 | 7.47 | 872 | 7.51 | 0.002 |
| D-penicillamine | 131 | 1.13 | 1298 | 1.11 | 0.002 |
| Azathioprine | 208 | 1.79 | 223 | 1.92 | 0.01 |
| Mycophenolate | 5 | 0.04 | 5 | 0.04 | 0.000 |
| Cyclosporine | 555 | 4.78 | 544 | 4.68 | 0.004 |
| Biological DMARDs | | | | | |
| Etanercept | 625 | 5.38 | 629 | 5.42 | 0.002 |
| Adalimumab | 198 | 1.70 | 193 | 1.66 | 0.003 |
| Types of acupuncture | | | | | |
| Manual acupuncture | – | – | 10 050 | 86.5 | |
| Electroacupuncture | – | – | 401 | 3.45 | |
| Combination of both types | – | – | 1162 | 10.0 | |
| Duration from rheumatoid arthritis diagnosis and index, days (mean, median) | (1078.52, 795.0) | | (1065.18, 707.0) | | 0.32 |
| Acupuncture visits (mean, median) | – | | (9.83, 3.00) | | |
| DMARDs, disease-modifying antirheumatic drugs; NSAID, non-steroidal anti-inflammatory drug. | | | | | |

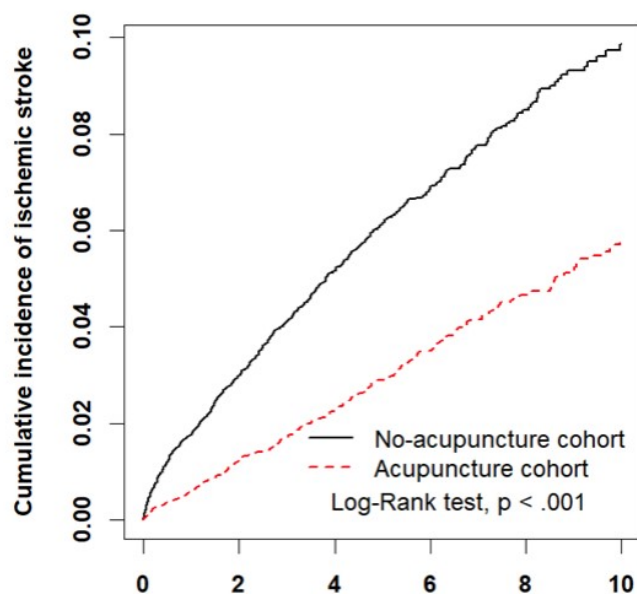


Figure 2 The cumulative incidence of ischaemic stroke in acupuncture (dashed line) cohort and the no-acupuncture cohort (solid line). Patients in the acupuncture group had a lower incidence of ischaemic stroke (log-rank test, $p < 0.001$).

There were no differences in the proportions of alcoholism, tobacco dependence, or obesity between the two cohorts. NSAIDs were the most common prescriptions in both cohorts, and 76% of the included patients were on these medications. In the participants of the two cohorts, 55% used oral steroids and 5% used statin agents. Most patients (87%) were treated by manual acupuncture, with electroacupuncture having been used in 3% of the participants; the remaining 10% had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischaemic stroke (online supplemental table 1). The incidence of ischaemic stroke in RA patients increased with age, with older patients having a higher risk. The adjusted SHRs in the 40- to 59-year-old group and the over 60-year-old group were 5.99 and 14.7, respectively. The patients with comorbidities of diabetes mellitus, hypertension and congestive heart failure had a higher risk of ischaemic stroke. The adjusted SHRs of the patients with diabetes mellitus, hypertension and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The cumulative incidence of ischaemic stroke was significantly lower in the acupuncture cohort (log-rank test, $p < 0.001$) (figure 2).

Online supplemental table 2 shows that the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the no-acupuncture cohort (12.4 per 1000 person-years) developed ischaemic stroke (adjusted SHR 0.57, 95% CI 0.50 to 0.65). Both males and females were observed to experience the benefit of ischaemic stroke prevention, with an adjusted SHR of 0.58 in

the female group (95% CI 0.49 to 0.67) and an adjusted SHR of 0.54 in the male group (95% CI 0.41 to 0.70). Patients in the age subgroup ≥ 40 years old had a lower risk of ischaemic stroke after acupuncture therapy (adjusted SHR 0.54, 95% CI 0.44 to 0.66 in the 40- to 59-year-old group; adjusted SHR 0.58, 95% CI 0.48 to 0.69 in the over 60-year-old group). Acupuncture decreased the risk of ischaemic stroke in most patients with comorbidities. Coprescriptions with steroids, statins or DMARDs did not change the positive results of acupuncture therapy.

The results from the non-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity score matching in online supplemental tables 3 and 4. The final results analysed by competing-risk regression models are compatible with the results after 1:1 propensity score matching.

DISCUSSION

To the best of our knowledge, this is the first study to show that acupuncture therapy is beneficial for ischaemic stroke prevention in RA patients. RA is one of the common disease categories among acupuncture visits in Taiwan.³¹ We previously found that 23.6% of RA patients had received acupuncture.²⁶ In the present study, we showed that the benefit of acupuncture therapy in reducing the risk of ischaemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have a high risk for the development of stroke, there is an unmet need to improve preventive measures for patients with RA.³² Inflammation is a consistent and independent predictor of cardiovascular disease in RA.³³ TNF- α is a cytokine that mediates inflammatory reactions.³⁴ A high level of TNF- α has been observed in RA patients, and it has been found that TNF- α can induce pannus formation and subsequent bone destruction.³⁵ By interrupting TNF- α expression and production by inflammatory cells, TNF- α inhibitors can efficiently control the inflammatory process.³⁶ Biological agents targeting cytokines may decrease cardiovascular disease risk in RA.³⁷ Therefore, it would be of interest to know whether acupuncture fits the niche to reduce inflammation in RA patients.

There are some evidence and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy,³⁸ relieving pain³⁹ and attenuating cardiovascular disease⁴⁰ in different clinical trials. Previous clinical studies revealed that acupuncture reduced the number of tender joints, relieved morning stiffness and joint pain, enhanced physical activity, and improved quality of life in patients with RA.^{41 42} In the analysis of blood and synovial fluid of RA patients, acupuncture was found to reduce TNF- α and vascular endothelial growth factor to improve the inflammation of RA.⁴³ In animal studies, acupuncture reduced inflammation in a collagen-induced arthritis model.^{44–46} Furthermore, acupuncture not only has analgesic effects through β -endorphin,⁴⁷ adenosine⁴⁸ and

orexin,⁴⁹ but also reduces inflammation through dopamine.⁵⁰ On the other hand, unstable blood pressure and lipid profiles are the two risk factors for ischaemic stroke, and acupuncture therapy has the advantage of controlling both hypertension and dyslipidaemia.^{51 52} If acupuncture relieves morning stiffness and joint pain, patients might also benefit from increasing daily activities, which might also reduce the risk of stroke.⁵³

Our study has some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we used prescriptions for RA treatment as variables that could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts were minimised. We had similar percentages of patients who used NSAIDs, steroid agents, statins, and DMARDs. The second limitation was that the RCIPD did not provide data on height, weight, laboratory data or exercise status. We tried to define a diagnosis of alcoholism, tobacco use, and obesity to represent these personal characteristics and lifestyles; then, through 1:1 propensity score matching, we attempted to eliminate or minimise confounders.⁵⁴ The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischaemic stroke prevention in patients with RA. The algorithm for risk of developing cardiovascular events, such as the Framingham Risk Score, is hard to formulate because of the lack of the above information. Additionally, the RCIPD database could not offer information on acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and expectations of the patients. Because of the standard TCM programme training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (online supplemental figure 1).^{55 56} Further clinical trials with standardised acupoints should be conducted based on the findings of this study. The difference in treatment results among various types of interventions could not be discovered in our database and was not included as a result measure. The evidence of the treatment dose of acupuncture therapy is still being established; thus, we did not discuss the topic here.

CONCLUSIONS

Our study demonstrates that the ischaemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. The possible mechanism may involve reducing proinflammatory cytokines through acupuncture therapy, thereby attenuating cardiovascular disease, including ischaemic stroke. The study also offers important ideas for more comprehensive research in the future.

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Authors' contributions CYH and MCH contributed equally as co-first authors. MCH contributed to the conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to the conception of the study, participated in the interpretation of clinical data and drafted the manuscript. HHL participated in the interpretation of clinical data and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the manuscript. MYW contributed to the design of the study, participated in the interpretation of clinical data and drafted the manuscript. YCL supervised the project, participated in the interpretation of clinical data and drafted the manuscript. HRY supervised the project, contributed to the conception and design of the study and finalised the manuscript. HRY is the guarantor. MYW and HRY contributed equally as co-corresponding authors.

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

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics Approval Statement The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH109-REC2-031(CR-3)).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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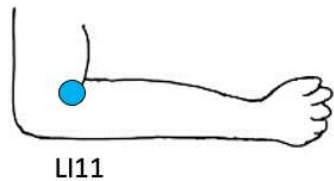
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REFERENCES

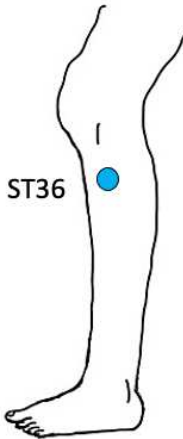
- Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990;16:513–37.
- Sesin CA, Bingham CO. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2005;35:185–96.
- Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762–84. 10.1002/art.23721 Available: <https://onlinelibrary.wiley.com/toc/15290131a/59/6>
- Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1010–4.
- Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
- Aviña-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008;59:1690–7.
- Aviña-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012;71:1524–9.
- de Groot L, Posthumus MD, Kallenberg CGM, et al. Risk factors and early detection of atherosclerosis in rheumatoid arthritis. *Eur J Clin Invest* 2010;40:835–42.
- Meune C, Touzé E, Trinquet L, et al. High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253–61.
- Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
- Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011;25:469–83.
- Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. *Arthritis Rheum* 2008;59:1090–6.
- Almutairi K, Nossent J, Preen D, et al. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int* 2021;41:863–77.
- Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: a population-based incidence cohort of patients with rheumatoid arthritis. *J Rheumatol* 2006;33:248–55.
- Lai CH, Lai MS, Lai KL, et al. Nationwide population-based epidemiologic study of rheumatoid arthritis in Taiwan. *Clin Exp Rheumatol* 2012;30:358–63.
- Liou T-H, Huang S-W, Lin J-W, et al. Risk of stroke in patients with rheumatism: a nationwide longitudinal population-based study. *Sci Rep* 2014;4:5110.
- Holmqvist M, Gränsmark E, Mantel A, et al. Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. *Ann Rheum Dis* 2013;72:541–6.
- Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. *Curr Treat Options Neurol* 2015;17:356.
- O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591–602.
- Bowman SJ. Hematological manifestations of rheumatoid arthritis. *Scand J Rheumatol* 2002;31:251–9.
- Seca S, Patricio M, Kirch S, et al. Effectiveness of acupuncture on pain, functional disability, and quality of life in rheumatoid arthritis of the hand: results of a double-blind randomized clinical trial. *J Altern Complement Med* 2019;25:86–97.
- Tam L-S, Leung P-C, Li TK, et al. Acupuncture in the treatment of rheumatoid arthritis: a double-blind controlled pilot study. *BMC Complement Altern Med* 2007;7:35.
- Bernateck M, Becker M, Schwake C, et al. Adjuvant auricular electroacupuncture and autogenic training in rheumatoid arthritis: a randomized controlled trial. Auricular acupuncture and autogenic training in rheumatoid arthritis. *Forsch Komplementmed* 2008;15:187–93.
- Chou PC, Chu HY. Clinical efficacy of acupuncture on rheumatoid arthritis and associated mechanisms: a systematic review. *Evid Based Complement Alternat Med* 2018;2018:8596918.
- Huang C-Y, Wu M-Y, Huang M-C, et al. The association between acupuncture therapies and reduced fracture risk in patients with osteoarthritis: a nationwide retrospective matched cohort study. *J Integr Complement Med* 2022;28:418–26.
- Huang M-C, Pai F-T, Lin C-C, et al. Characteristics of traditional Chinese medicine use in patients with rheumatoid arthritis in Taiwan: a nationwide population-based study. *J Ethnopharmacol* 2015;176:9–16.
- Shih C-C, Liao C-C, Sun M-F, et al. A retrospective cohort study comparing stroke recurrence rate in ischemic stroke patients with and without acupuncture treatment. *Medicine (Baltimore)* 2015;94:e1572.
- Huang C-Y, Wu M-Y, Chang C-L, et al. Coprescription trends in Western medicine, Chinese Herbal medicine and dental medicine among older adults in Taiwan from 1997 to 2013. *Complement Ther Med* 2021;63:102782.
- Huang C-Y, Wu M-Y, Kuo Y-H, et al. Chinese herbal medicine is helpful for survival improvement in patients with multiple myeloma in Taiwan: a nationwide retrospective matched-cohort study. *Integr Cancer Ther* 2020;19:1–10.
- Wu M-Y, Huang M-C, Liao H-H, et al. Acupuncture decreased the risk of coronary heart disease in patients with rheumatoid arthritis in Taiwan: a nationwide propensity score-matched study. *BMC Complement Altern Med* 2018;18:341.
- Wu M-Y, Lee Y-C, Lin C-L, et al. Trends in use of acupuncture among adults in Taiwan from 2002 to 2011: a nationwide population-based study. *PLoS One* 2018;13:e0195490.
- Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;76:17–28.
- Karpouzias GA, Ormseth SR, Hernandez E, et al. Impact of cumulative inflammation, cardiac risk factors, and medication exposure on coronary atherosclerosis progression in rheumatoid arthritis. *Arthritis Rheumatol* 2020;72:400–8. 10.1002/art.41122 Available: <https://acrjournals.onlinelibrary.wiley.com/toc/23265205/72/3>
- Visvanathan S, Rahman MU, Keystone E, et al. Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: results from the GO-FORWARD study. *Arthritis Res Ther* 2010;12:R211.
- Kleinert S, Tony H-P, Krause A, et al. Impact of patient and disease characteristics on therapeutic success during adalimumab treatment of patients with rheumatoid arthritis: data from a German noninterventional observational study. *Rheumatol Int* 2012;32:2759–67.
- Wijbrandts CA, Dijkgraaf MGW, Kraan MC, et al. The clinical response to Infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour necrosis factor alpha expression in the synovium. *Ann Rheum Dis* 2008;67:1139–44.
- Karpouzias GA, Ormseth SR, Hernandez E, et al. Biologics may prevent cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque formation and stabilizing high-risk lesions. *Arthritis Rheumatol* 2020;72:1467–75. 10.1002/art.41293 Available: <https://acrjournals.onlinelibrary.wiley.com/toc/23265205/72/9>

- 38 Bao T, Patil S, Chen C, *et al.* Effect of acupuncture vs sham procedure on chemotherapy-induced peripheral neuropathy symptoms: a randomized clinical trial. *JAMA Netw Open* 2020;3:e200681.
- 39 Zhao L, Chen J, Li Y, *et al.* The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med* 2017;177:508–15.
- 40 Zhao L, Li D, Zheng H, *et al.* Acupuncture as adjunctive therapy for chronic stable angina: a randomized clinical trial. *JAMA Intern Med* 2019;179:1388–97.
- 41 Wang R, Jiang C, Lei Z, *et al.* The role of different therapeutic courses in treating 47 cases of rheumatoid arthritis with acupuncture. *J Tradit Chin Med* 2007;27:103–5.
- 42 Lee H, Lee J-Y, Kim Y-J, *et al.* Acupuncture for symptom management of rheumatoid arthritis: a pilot study. *Clin Rheumatol* 2008;27:641–5.
- 43 Ouyang B-S, Gao J, Che J-L, *et al.* Effect of electro-acupuncture on tumor necrosis factor-alpha and vascular endothelial growth factor in peripheral blood and joint synovia of patients with rheumatoid arthritis. *Chin J Integr Med* 2011;17:505–9.
- 44 He X, Huang L, Qiu S, *et al.* Beta-endorphin attenuates collagen-induced arthritis partially by inhibiting peripheral pro-inflammatory mediators. *Exp Ther Med* 2018;15:4014–8.
- 45 Ye T-S, Du Z-H, Li Z-H, *et al.* Repeated electroacupuncture persistently elevates adenosine and ameliorates collagen-induced arthritis in rats. *Evid Based Complement Alternat Med* 2016;2016:3632168.
- 46 Li J, Li J, Chen R, *et al.* Targeting NF-kappa beta and TNF-alpha activation by electroacupuncture to suppress collagen-induced rheumatoid arthritis in model rats. *Altern Ther Health Med* 2015;21:26–34.
- 47 Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. *Trends Neurosci* 2003;26:17–22.
- 48 Goldman N, Chen M, Fujita T, *et al.* Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture. *Nat Neurosci* 2010;13:883–8.
- 49 Chen Y-H, Lee H-J, Lee MT, *et al.* Median nerve stimulation induces analgesia via orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. *Proc Natl Acad Sci U S A* 2018;115:E10720–9.
- 50 Torres-Rosas R, Yehia G, Peña G, *et al.* Dopamine mediates vagal modulation of the immune system by electroacupuncture. *Nat Med* 2014;20:291–5.
- 51 Hsieh CH. The effects of auricular acupressure on weight loss and serum lipid levels in overweight adolescents. *Am J Chin Med* 2010;38:675–82.
- 52 Flachskampf FA, Gallasch J, Gefeller O, *et al.* Randomized trial of acupuncture to lower blood pressure. *Circulation* 2007;115:3121–9.
- 53 Semb AG, Ikdahl E, Wibetoe G, *et al.* Atherosclerotic cardiovascular disease prevention in rheumatoid arthritis. *Nat Rev Rheumatol* 2020;16:361–79.
- 54 Rassen JA, Shelat AA, Myers J, *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf* 2012;21 Suppl 2:69–80.
- 55 Tou SI, Huang CY, Yen HR. Effect of acupoint stimulation on controlling pain from heel lance in neonates: a systematic review and meta-analysis of randomized controlled trials. *Children (Basel)* 2023;10:1024.
- 56 Lin JG, Li TM, Hsu SF. *Newly Edited Color Book of Acupuncture and Moxibustion*. Taipei, Taiwan: JYIN Publishing Company, 2009.

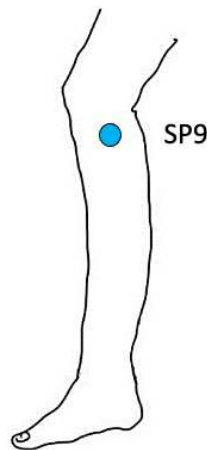
A



B



C



Supplementary Table 1. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with acupuncture treatment and covariates among rheumatoid arthritis patients using the competing-risks regression models.

| Variable | No. of event (n = 946) | Crude* | | | Adjusted† | | |
|--|------------------------------|--------|--------------|---------|-----------|--------------|---------|
| | | SHR | (95% CI) | p-value | SHR | (95% CI) | p-value |
| Acupuncture treatment | | | | | | | |
| No | 605 | 1.00 | reference | | 1.00 | reference | |
| Yes | 341 | 0.52 | (0.46, 0.60) | <0.001 | 0.57 | (0.49, 0.65) | <0.001 |
| Sex | | | | | | | |
| Women | 714 | 1.00 | reference | | 1.00 | reference | |
| Men | 231 | 1.44 | (1.24, 1.67) | <0.001 | 1.32 | (1.14, 1.54) | <0.001 |
| Age group | | | | | | | |
| 18-39 | 13 | 1.00 | reference | | 1.00 | reference | |
| 40-59 | 372 | 7.17 | (4.14, 12.4) | <0.001 | 5.99 | (3.44, 10.4) | <0.001 |
| ≥ 60 | 561 | 28.1 | (16.3, 48.6) | <0.001 | 14.7 | (8.38, 25.7) | <0.001 |
| Baseline Comorbidity (ref = no comorbidity) | | | | | | | |
| Diabetes mellitus | 334 | 2.64 | (2.31, 3.01) | <0.001 | 1.58 | (1.36, 1.82) | <0.001 |
| Hypertension | 654 | 3.96 | (3.45, 4.54) | <0.001 | 2.10 | (1.79, 2.47) | <0.001 |
| Hyperlipidemia | 371 | 1.94 | (1.70, 2.21) | <0.001 | 1.08 | (0.93, 1.25) | 0.30 |
| Congestive heart failure | 148 | 3.18 | (2.67, 3.79) | <0.001 | 1.31 | (1.08, 1.59) | 0.006 |

| | | | | | | | |
|---------------------|------|------|--------------|----------|------|--------------|----------|
| Depression | 120 | 1.46 | (1.21, 1.77) | <0.001 | 1.12 | (0.91, 1.37) | 0.28 |
| Anxiety | 256 | 1.40 | (1.21, 1.61) | <0.001 | 0.99 | (0.85, 1.16) | 0.94 |
| Alcoholism | 20 | 1.48 | (0.95, 2.29) | 0.08 | 1.46 | (0.88, 2.43) | 0.14 |
| Tobacco use | 2 | 0.55 | (0.14, 2.20) | 0.40 | 0.32 | (0.07, 1.40) | 0.13 |
| Obesity | 10 | 1.16 | (0.62, 2.17) | 0.65 | 1.10 | (0.58, 2.08) | 0.77 |
| Atrial fibrillation | 50 | 1.02 | (0.77, 1.35) | 0.90 | 0.89 | (0.66, 1.19) | 0.43 |
| Drugs used | | | | | | | |
| Oral steroid | 1621 | 0.57 | (0.47-0.69) | < 0.0001 | 0.51 | (0.42-0.62) | < 0.0001 |
| NSAID | 1726 | 0.22 | (0.11-0.46) | < 0.0001 | 0.24 | (0.11-0.51) | 0.0002 |
| Statin | 329 | 1.04 | (0.92-1.17) | 0.5575 | 0.65 | (0.58-0.74) | < 0.0001 |
| Conventional DMARDS | | | | | | | |
| Hydroxychloroquine | 333 | 0.47 | (0.41, 0.54) | <0.001 | 0.70 | (0.60, 0.81) | <0.001 |
| Sulfasalazine | 235 | 0.47 | (0.41, 0.54) | <0.001 | 0.80 | (0.68, 0.94) | 0.007 |
| Methotrexate | 2 | 1.88 | (0.50, 7.04) | 0.35 | 3.15 | (0.84, 11.9) | 0.08 |
| Leflunomide | 18 | 0.22 | (0.14, 0.35) | <0.001 | 0.34 | (0.22, 0.54) | <0.001 |
| D-penicillamine | 11 | 0.85 | (0.46, 1.53) | 0.53 | 1.07 | (0.61, 1.88) | 0.05 |
| Azathioprine | 9 | 0.39 | (0.20, 0.75) | 0.004 | 0.77 | (0.40, 1.49) | 0.44 |
| Mycophenolate | 0 | - | - | | - | - | |
| Cyclosporine | 35 | 0.62 | (0.44, 0.87) | 0.005 | 1.40 | (0.99, 1.98) | 0.06 |
| Biological DMARDs | | | | | | | |
| Etanercept | 16 | 0.27 | (0.16, 0.44) | <0.001 | 0.51 | (0.31, 0.83) | 0.007 |
| Adalimumab | 3 | 0.18 | (0.06, 0.57) | 0.003 | 0.43 | (0.14, 1.34) | 0.15 |

Crude SHR^{*} represents the relative subhazard ratio;

Adjusted SHR[†] represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in competing-risks regression models.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

Supplementary Table 2. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities, and drug used using the competing-risks regression models.

| Variables | Rheumatoid arthritis | | | | | | Compared with no-acupuncture users | |
|----------------------|----------------------|--------------|-----------------|-------------|--------------|-----------------|------------------------------------|---------------------|
| | No | | | Yes | | | Crude SHR | Adjusted SHR |
| | (n = 11613) | | | (n = 11613) | | | | |
| | Event | Person years | IR [†] | Event | Person years | IR [†] | (95% CI) | (95% CI) |
| Total | 605 | 48836 | 12.4 | 341 | 57273 | 5.95 | 0.52(0.46, 0.60)*** | 0.57(0.50, 0.65)*** |
| Sex | | | | | | | | |
| Women | 460 | 40274 | 11.4 | 254 | 46907 | 5.41 | 0.51(0.44, 0.60)*** | 0.58(0.49, 0.67)*** |
| Men | 145 | 8562 | 16.9 | 87 | 10366 | 8.39 | 0.54(0.42, 0.71)*** | 0.54(0.41, 0.70)*** |
| Age group | | | | | | | | |
| 18-39 | 5 | 8734 | 0.57 | 8 | 8576 | 0.93 | 1.47(0.49, 4.45) | 1.45(0.44, 4.76) |
| 40-59 | 226 | 29529 | 7.65 | 146 | 37225 | 3.92 | 0.53(0.43, 0.66)*** | 0.54(0.44, 0.66)*** |
| ≥ 60 | 374 | 10573 | 35.4 | 187 | 11472 | 16.3 | 0.55(0.46, 0.65)*** | 0.58(0.48, 0.69)*** |
| Baseline Comorbidity | | | | | | | | |
| Diabetes mellitus | | | | | | | | |
| No | 383 | 41083 | 9.32 | 229 | 48060 | 4.76 | 0.55(0.47, 0.65)*** | 0.60(0.51, 0.71)*** |
| Yes | 222 | 7753 | 28.6 | 112 | 9213 | 12.2 | 0.47(0.38, 0.59)*** | 0.52(0.41, 0.65)*** |
| Hypertension | | | | | | | | |

| | | | | | | | | |
|--------------------------|-----|-------|------|-----|-------|------|---------------------|---------------------|
| No | 184 | 32174 | 5.72 | 108 | 37634 | 2.87 | 0.52(0.41, 0.66)*** | 0.57(0.45, 0.72)*** |
| Yes | 421 | 16661 | 25.3 | 233 | 19639 | 11.9 | 0.53(0.45, 0.62)*** | 0.57(0.49, 0.67)*** |
| Hyperlipidemia | | | | | | | | |
| No | 366 | 36970 | 9.90 | 209 | 43496 | 4.81 | 0.53(0.45, 0.62)*** | 0.61(0.51, 0.72)*** |
| Yes | 239 | 11866 | 20.1 | 132 | 13777 | 9.58 | 0.51(0.41, 0.63)*** | 0.51(0.41, 0.63)*** |
| Congestive heart failure | | | | | | | | |
| No | 513 | 46595 | 11.0 | 285 | 54590 | 5.22 | 0.51(0.44, 0.59)*** | 0.55(0.47, 0.64)*** |
| Yes | 92 | 2241 | 41.1 | 56 | 2683 | 20.9 | 0.61(0.44, 0.85)*** | 0.65(0.47, 0.92)*** |
| Depression | | | | | | | | |
| No | 523 | 44638 | 11.7 | 303 | 52396 | 5.78 | 0.54(0.47, 0.62)*** | 0.59(0.51, 0.67)*** |
| Yes | 82 | 4198 | 19.5 | 38 | 4877 | 7.79 | 0.43(0.30, 0.64)*** | 0.48(0.32, 0.72)*** |
| Anxiety | | | | | | | | |
| No | 442 | 38718 | 11.4 | 248 | 46073 | 5.38 | 0.51(0.44, 0.60)*** | 0.56(0.48, 0.66)*** |
| Yes | 163 | 10117 | 16.1 | 93 | 11200 | 8.30 | 0.55(0.43, 0.71)*** | 0.57(0.44, 0.74)*** |
| Alcoholism | | | | | | | | |
| No | 596 | 48177 | 12.4 | 330 | 56529 | 5.84 | 0.51(0.45, 0.59)*** | 0.56(0.49, 0.64)*** |
| Yes | 9 | 659 | 13.7 | 11 | 744 | 14.8 | 1.12(0.47, 2.67) | 1.25(0.50, 3.09) |
| Tobacco use | | | | | | | | |
| No | 603 | 48655 | 12.4 | 341 | 57090 | 5.97 | 0.52(0.46, 0.60)*** | 0.57(0.50, 0.65)*** |
| Yes | 2 | 181 | 11.1 | 0 | 182 | 0.00 | | |
| Obesity | | | | | | | | |
| No | 598 | 48412 | 12.4 | 338 | 56737 | 5.96 | 0.52(0.46, 0.60)*** | 0.57(0.50, 0.65)*** |

| | | | | | | | | |
|---------------------|-----|-------|------|-----|-------|------|---------------------|---------------------|
| Yes | 7 | 424 | 16.5 | 3 | 536 | 5.60 | 0.38(0.10, 1.49) | 0.40(0.14, 1.19) |
| Atrial fibrillation | | | | | | | | |
| No | 576 | 46291 | 12.4 | 320 | 54553 | 5.87 | 0.51(0.45, 0.59)*** | 0.56(0.49, 0.64)*** |
| Yes | 29 | 2545 | 11.4 | 21 | 2720 | 7.72 | 0.72(0.41, 1.26) | 0.70(0.38, 1.30) |
| Drugs used | | | | | | | | |
| Oral steroid | | | | | | | | |
| No | 318 | 17828 | 17.8 | 166 | 21844 | 7.60 | 0.48(0.40, 0.58)*** | 0.53(0.44, 0.64)*** |
| Yes | 287 | 31008 | 9.26 | 175 | 35429 | 4.94 | 0.56(0.46, 0.68)*** | 0.59(0.49, 0.72)*** |
| NSAID | | | | | | | | |
| No | 216 | 7329 | 29.5 | 105 | 9509 | 11.0 | 0.46(0.37, 0.58)*** | 0.54(0.43, 0.69)*** |
| Yes | 389 | 41506 | 9.37 | 236 | 47764 | 4.94 | 0.55(0.47, 0.64)*** | 0.56(0.48, 0.66)*** |
| Statin | | | | | | | | |
| No | 586 | 45820 | 12.8 | 322 | 54040 | 5.96 | 0.51(0.44, 0.58)*** | 0.56(0.49, 0.64)*** |
| Yes | 19 | 3016 | 6.30 | 19 | 3233 | 5.88 | 0.94(0.50, 1.79) | 0.97(0.49, 1.95) |
| Conventional DMARDS | | | | | | | | |
| No | 347 | 14099 | 24.6 | 181 | 18431 | 9.82 | 0.48(0.40, 0.57)*** | 0.54(0.45, 0.65)*** |
| Yes | 258 | 34736 | 7.43 | 160 | 38842 | 4.12 | 0.56(0.46, 0.68)*** | 0.58(0.47, 0.71)*** |
| Biological DMARDs | | | | | | | | |
| No | 591 | 44821 | 13.2 | 336 | 52599 | 6.39 | 0.53(0.46, 0.60)*** | 0.58(0.50, 0.66)*** |
| Yes | 14 | 4014 | 3.49 | 5 | 4674 | 1.07 | 0.28(0.10, 0.79)* | 0.26(0.09, 0.80)** |

Abbreviation: IR, incidence rate per 1,000 person-years; SHR, subhazard ratio; CI, confidence interval

Adjusted SHR: adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in the competing-risks regression models.

*: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

Supplementary Table 3. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching. .

| Variable | Rheumatoid Arthritis | | | | Standardized mean difference |
|--------------------------|-----------------------|------|-----------------|------|------------------------------------|
| | Acupuncture treatment | | | | |
| | No (n = 22218) | | Yes (n = 12266) | | |
| | n | % | n | % | |
| Sex | | | | | |
| Women | 16702 | 75.2 | 10109 | 82.4 | 0.01 |
| Men | 5516 | 24.8 | 2157 | 17.6 | 0.18 |
| Age group | | | | | |
| 18-39 | 2994 | 13.5 | 1767 | 14.4 | 0.03 |
| 40-59 | 12351 | 55.6 | 7762 | 63.3 | 0.16 |
| ≥ 60 | 6873 | 30.9 | 2737 | 22.3 | 0.20 |
| Mean ± SD (years) | 56.7±14.7 | | 54.3±13.3 | | 0.17 |
| Baseline Comorbidity | | | | | |
| Diabetes mellitus | 4117 | 18.5 | 2260 | 18.4 | 0.003 |
| Hypertension | 8857 | 39.9 | 4632 | 37.8 | 0.04 |
| Hyperlipidemia | 5610 | 25.3 | 3593 | 29.3 | 0.09 |
| Congestive heart failure | 1698 | 7.64 | 736 | 6.00 | 0.07 |
| Depression | 1901 | 8.56 | 1394 | 11.4 | 0.09 |
| Anxiety | 4591 | 20.7 | 3118 | 25.4 | 0.11 |
| Alcoholism | 422 | 1.90 | 244 | 1.99 | 0.01 |
| Tobacco use | 146 | 0.66 | 84 | 0.68 | 0.003 |
| Obesity | 188 | 0.85 | 163 | 1.33 | 0.05 |
| Atrial fibrillation | 1102 | 4.96 | 845 | 6.89 | 0.08 |
| Drugs used | | | | | |
| Oral steroid | 6489 | 55.6 | 6495 | 55.9 | 0.001 |
| NSAID | 8823 | 76.0 | 8882 | 76.5 | 0.012 |
| Statin | 5592 | 5.10 | 593 | 5.11 | 0.000 |
| Conventional DMARDS | | | | | |
| Hydroxychloroquine | 9299 | 41.9 | 6059 | 49.4 | 0.15 |
| Sulfasalazine | 7210 | 32.5 | 4606 | 37.6 | 0.11 |
| Methotrexate | 14 | 0.06 | 11 | 0.09 | 0.01 |
| Leflunomide | 1309 | 5.89 | 973 | 7.93 | 0.08 |
| D-penicillamine | 196 | 0.88 | 138 | 1.13 | 0.02 |
| Azathioprine | 385 | 1.73 | 229 | 1.87 | 0.01 |
| Mycophenolate | 10 | 0.05 | 7 | 0.06 | 0.01 |
| Cyclosporine | 816 | 3.67 | 594 | 4.84 | 0.06 |

| | | | | | |
|--|-----|----------------|------------------|-------|-------|
| Biological DMARDs | | | | | |
| Etanercept | 625 | 5.38 | 629 | 5.42 | 0.002 |
| Adalimumab | 198 | 1.70 | 193 | 1.66 | 0.003 |
| Types of acupuncture | | | | | |
| Manual acupuncture | - | - | 10604 | 86.45 | |
| Electroacupuncture | - | - | 407 | 3.32 | |
| Combination of both types | - | - | 1255 | 10.23 | |
| Duration from rheumatoid arthritis diagnosis and index, days (mean, median) | | | | | |
| Acupuncture visits (mean, median) | | | | | |
| | | (981.29, 6680) | (1047.36, 688.5) | 0.32 | |
| | | - | (10.43, 3.00) | | |

The mean (median) follow-up period was 4.96 (4.39) and 4.01 (3.17) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in un-matching.

| Variable | No. of event (n = 1441) | Crude* | | | Adjusted† | | |
|----------------------|----------------------------|--------|--------------|---------|-----------|--------------|---------|
| | | SHR | (95% CI) | p-value | SHR | (95% CI) | p-value |
| Accepted Acupuncture | | | | | | | |
| No | 1080 | 1.00 | reference | | 1.00 | reference | |
| Yes | 361 | 0.48 | (0.42, 0.53) | <0.001 | 0.65 | (0.58, 0.74) | <0.001 |

Crude SHR^{*} represented relative subhazard ratio;
Adjusted SHR[†] represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, comorbidities, and drugs used in competing-risks regression models.

Acupuncture may curb heightened risk of stroke associated with rheumatoid arthritis

Effects independent of sex, age, medication use, and co-existing conditions

Needling may reduce pro-inflammatory proteins in the body, suggest researchers

A course of acupuncture may curb the heightened risk of stroke associated with rheumatoid arthritis, finds a comparative study published in the open access journal **BMJ Open**.

The effects seem to be independent of sex, age, medication use, and co-existing conditions, the findings indicate, prompting the researchers to suggest that the procedure may reduce levels of pro-inflammatory proteins (cytokines) in the body that are linked to cardiovascular disease.

The principal cause of death in people with rheumatoid arthritis is cardiovascular disease. And they are more likely to have a stroke than the general population, note the researchers.

Acupuncture is already used to control pain and dampen down inflammation, and the researchers wanted to find out if it might also lower the risk of ischaemic stroke—caused by a blood clot in the brain—that is associated with systemic inflammation.

They drew on national medical records from the Registry for Catastrophic Illness Patients Database (RCIPD), for 47,809 adults newly diagnosed with rheumatoid arthritis between 1997 and 2010.

The final analysis included 23,226 patients with complete data, 12,266 of whom were treated with acupuncture following their diagnosis up until the end of December 2010.

Of these, 11,613 were each matched for age, sex, co-existing conditions—diabetes, high blood pressure, high blood fats, congestive heart failure, anxiety/depression, obesity, atrial fibrillation, alcohol dependency, and smoking—medication use—non-steroidal anti-inflammatory drugs, statins, and disease modifying drugs—and year of diagnosis with a patient who hadn't been treated with acupuncture.

Women, those aged 40–59, and participants with high blood pressure predominated in both groups.

Most (87%) of those in the acupuncture group were treated with manual acupuncture (87%); 3% were treated with electroacupuncture, whereby an electrode producing a low pulse of electricity is attached to the needle; and 10% received both types.

On average, 1065 days elapsed between a rheumatoid arthritis diagnosis and receipt of the first acupuncture treatment, with the number of treatments averaging around 10 in total.

During the monitoring period up to the end of 2011, 946 patients had an ischaemic stroke. Unsurprisingly, risk rose in tandem with increasing age, and with the number of co-existing conditions.

Those with high blood pressure, for example, were more than twice as likely to have a stroke as those with normal blood pressure, while those with diabetes were 58% more likely to do so.

But there were significantly fewer cases of ischaemic stroke among the acupuncture group: 341 vs 605, equivalent to a 43% lower risk. And this was independent of age, sex, medication use, and co-existing conditions.

This is an observational study, and as such, no firm conclusions can be drawn about cause and effect, and the researchers also acknowledge that they were only able to estimate disease severity from the drugs the patients took.

Nor did they have information on potentially influential factors, such as height, weight, lab tests or physical activity levels, and not everyone would have had the same pressure points needled, they add.

But they point out: "Inflammation is a consistent and independent predictor of cardiovascular disease in [rheumatoid arthritis]," so acupuncture may lower pro-inflammatory proteins, thereby reducing the risk of cardiovascular disease, including ischaemic stroke, they suggest.

"Unstable blood pressure and lipid profiles are the two risk factors for ischaemic stroke, and acupuncture therapy has the advantage of controlling both hypertension and dyslipidaemia," they explain, adding: "If acupuncture relieves morning stiffness and joint pain, patients might also benefit from increasing daily activities, which might also reduce the risk of stroke."