

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

BMJ Open

Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-075218
Article Type:	Original research
Date Submitted by the Author:	30-Apr-2023
Complete List of Authors:	Huang, Chia-Yu; China Medical University, Huang, Ming-Cheng; China Medical University Hospital, Department of Chinese Medicine Liao, Hou-Hsun; China Medical University Lin, Cheng-Li; China Medical University Hospital; China Medical University Lee, Yu-Chen; China Medical University, Graduate Institute of Acupuncture Science; China Medical University Hospital, Acupuncture Department Zimmerman, Gregory; China Medical University Wu, Mei-Yao; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of
Keywords:	Stroke < NEUROLOGY, COMPLEMENTARY MEDICINE, RHEUMATOLOGY
	·

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
2U 21	
∠ I כר	
∠∠ วว	
∠⊃ 21	
24	
25	
20	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
ک⊂ ⊿	
54 55	
55 56	
50	
57 58	
50	
60	
00	

1	Acupuncture decreased the risk of ischemic stroke in patients with
2	rheumatoid arthritis: a nationwide propensity score-matched study
3	
4	Authors:
5	Chia-Yu Huang, M.D., M.S. ^{1,2†} , Ming-Cheng Huang, M.D. ^{1,3†} , Hou-Hsun Liao, M.D.,
6	M.S. ^{2,3} , Cheng-Li Lin, M.S. ^{4,5} , Yu-Chen Lee, M.D., Ph.D. ^{3,6} , Gregory Zimmerman,
7	M.S. ⁶ , Mei-Yao Wu, M.D., Ph.D. ^{3,7,8,††} , Hung-Rong Yen, M.D., Ph.D. ^{1,3,8,9,10,††}
8	[†] Chia-Yu Huang and Ming-Cheng Huang contributed equally to this work and share
9	first authorship.
10	[†] [†] Mei-Yao Wu and Hung-Rong Yen contributed equally to this work and share
11	corresponding authorship.
12	
13	Affiliations:
14	¹ Department of Family Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi
15	Medical Foundation, Taichung, Taiwan
16	² Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of
17	Chinese Medicine, China Medical University, Taichung, Taiwan
18	³ Department of Chinese Medicine, China Medical University Hospital, Taichung,
19	Taiwan
20	⁴ Management Office for Health Data, China Medical University Hospital, Taichung,
21	Taiwan.
22	⁵ College of Medicine, China Medical University, Taichung, Taiwan
23	⁶ Graduate Institute of Acupuncture Science, College of Chinese Medicine, China
24	Medical University
25	⁷ School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine,
26	China Medical University, Taichung, Taiwan

BMJ Open

2		
3 4 5	1	⁸ Research Center for Traditional Chinese Medicine, Department of Medical Research,
6 7	2	China Medical University Hospital, Taichung, Taiwan
8 9	3	⁹ Chinese Medicine Research Center, China Medical University, Taichung, Taiwan
10 11	4	
12 13 14	5	Corresponding authors:
15 16	6	Hung-Rong Yen, M.D., Ph.D.
17 18	7	School of Chinese Medicine, College of Chinese Medicine, China Medical University,
19 20	8	Taichung, Taiwan
21 22 22	9	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
23 24 25	10	Tel.: +886-4-22053366 ext. 3313
26 27	11	Fax: +886-4-22365141
28 29	12	E-mail: hungrongyen@mail.cmu.edu.tw
30 31 32	13	or
33 34	14	Mei-Yao Wu, M.D., Ph.D.
35 36	15	School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, China
37 38	16	Medical University, Taichung, Taiwan
39 40 41	17	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
42 43	18	Tel.: +886-4-22052121 ext. 4561
44 45	19	Fax: +886-4-22365141
46 47	20	E-mail: meiyaowu0919@gmail.com
48 49 50	21	
50 51 52	22	E-mail addresses for all authors:
53 54	23	Chia-Yu Huang: dochuangcharlie@gmail.com
55 56	24	Ming-Cheng Huang: mchuang1128@gmail.com
57 58 59	25	Hou-Hsun Liao: a202098@cmu.edu.tw
60	26	Cheng-Li Lin: orangechengli@gmail.com

1	Yu-Chen Lee: d5167@mail.cmuh.org.tw
2	Gregory Zimmerman: gregzlac@gmail.com
3	Mei-Yao Wu: meiyaowu0919@gmail.com
4	Hung-Rong Yen: hungrongyen@mail.cmu.edu.tw
5	
6	Running title: Acupuncture Reduced the Risk of Stroke
7	
8	Word count: Abstract: 265; Text: 2354; No of Tables: 3; No of Figures: 2
9	
10	Keywords: Acupuncture; Cardiovascular diseases; National Health Insurance
11	Research Database; Rheumatoid arthritis; Stroke.
12	
13	Competing Interests: The authors declare that the research was conducted in the
14	absence of any commercial or financial relationships that could be construed as a
15	potential conflict of interest.
16	
17	Funding
18	This work was financially supported by the "Chinese Medicine Research Center,
19	China Medical University" from the Featured Areas Research Center Program within
20	the framework of the Higher Education Sprout Project by the Ministry of Education
21	(MOE) in Taiwan (CMRC-CHM-1). This study was also supported in part by China
22	Medical University (CMU103-BC-4-2, CMU105-BC-1-1, CMU105-BC-1-2), China
23	Medical University Hospital (DMR-107-011, DMR-110-002, and DMR-111-105),
24	and Ministry of Science and Technology (MOST108-2638-B-039-001-MY2,
24 25	and Ministry of Science and Technology (MOST108-2638-B-039-001-MY2, MOST107-2320-B-039-037, MOST108-2320-B-039-021, and MOST110-2321-B-

Page 5 of 43

1

BMJ Open

2
3
4
5
6
7
/
8
9
10
11
12
13
14
14
15
16
17
18
19
20
21
22
∠∠ 22
23
24
25
26
27
28
29
20
21
31
32
33
34
35
36
37
38
20
27
40
41
42
43
44
45
46
Δ 17
4/
48
49
50
51
52
53
54
55
55
50
57
58
59

60

Welfare Clinical Trial Center (MOHW110-TDU-B-212-124004), Taiwan. None of
 the funders and institutions listed had a role in the design and conduct of the study;
 collection, management, analysis, and interpretation of the data; preparation, review,
 or approval of the manuscript; and decision to submit the manuscript for publication.

6 Acknowledgement

5

This study was based in part on data from the National Health Insurance Research
Database, provided by the National Health Insurance Administration, Ministry of
Health and Welfare, and managed by National Health Research Institutes. The
interpretation and conclusions contained herein do not represent those of National
Health Insurance Administration, Ministry of Health and Welfare, or National Health
Research Institutes.

1 Abstract

 Objectives: The purpose of this study was to demonstrate that acupuncture is
beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid
arthritis (RA).

Design: This is a propensity score-matched cohort study.

Setting: This is a nationwide population-based study.

Participants: The patients with RA diagnosed between 1 January 1997 and 31
December 2010 through the National Health Insurance Research Database.

9 Interventions: The patients who were administered acupuncture therapy from the
10 initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were
11 included in the acupuncture cohort. Patients who did not receive acupuncture
12 treatment during the same time interval were regarded as 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
IS between these two cohorts through competing-risks regression models.

Results: After a 1:1 propensity score match, a total of 23,226 patients were identified. The basic characteristics of these patients were similar. A lower cumulative incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, p < 0.001). In the end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

24 Conclusions: This study showed the beneficial effect of acupuncture in reducing the25 incidence rate of ischemic stroke in patients with RA.

1 2		
3 4	1	Strengths and limitations of this study:
5 6 7	2	• Our research disclose the possible long-term effect from acupuncture in stroke
8 9	3	prevention which could not be investigated from clinical trial.
10 11 12	4	• The causality could not be proved directly as clinical trial through our study design.
12 13 14	5	
15 16	6	
17 18 10	7	
20 21	8	
22 23	9	
24 25	10	
26 27	11	
28 29 30	12	
31 32	13	
33 34	14	
35 36	15	
37 38 30	16	
40 41	17	
42 43	18	
44 45	19	
40 47 48	20	
49 50	21	
51 52	22	
53 54	23	
55 56 57	24	
57 58 59	25	
60	26	6

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness.¹ The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD).²⁻⁵ Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke.⁶⁻¹¹ Comparing to general population, stroke is more common noted in the RA patients.¹² The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively.¹³⁻¹⁵ But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29).¹⁶⁻¹⁷

Trying to disclose the agents to prevent stoke is an essential issue to clinical doctors and patients.¹⁸ The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF- α inhibitor) and anakinra (IL-1 inhibitor).^{3,5,19} And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients.¹⁸ But some of them could bring the complications in the bone marrow to cause thrombocytopenia.²⁰ The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, 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

BMJ Open

founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture.²⁶ Furthermore, secondary stoke prevention is also noted from acupuncture therapy in the Taiwanese.²⁷ And the hypothesis in the acupuncture to lower stoke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population.²⁸ In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database.²⁹ We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

Materials and Methods

2 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. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or 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 a 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 (CMUH104-REC2-115).

21 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 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had Page 11 of 43

BMJ Open

incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA 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 minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient 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 no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

17 Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and \geq 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401-405), hyperlipidemia (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 ischemic
 stroke (ICD-9-CM: 433-438) were compared between acupuncture and
 non-acupuncture cohort of RA patients.

6 Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including
manual acupuncture of the TCM type (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 standardized 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 less than 0.1 standard deviation (SD). A competing-risks regression models was 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 ischemic 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.

1 Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (Fig. 1). The baseline characteristics of both cohorts are presented in Table 1, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% 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, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

During the follow-up period, 946 patients developed ischemic stroke (**Table 2**). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The cumulative incidence of ischemic stroke

BMJ Open

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

was significantly lower in the acupuncture cohort (log-rank test, p < 0.001, Fig. 2).

Table 3 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50-0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥ 40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44-0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48-0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in Supplementary Table 1and 2. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching.

1 Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the 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 ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA.³² Inflammation is a consistent and independent predictor of CVD in RA.³³ TNF- α is a cytokine that mediates inflammation 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 CVD risk in RA.37 Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

There are a couple evidences 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 amounts 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 the RA patients, acupuncture was found to reduce TNF- α and vascular endothelial growth factor to improve the inflammation of RA.⁴³ In animal

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

studies, acupuncture reduced inflammation in collagen-induced arthritis model.⁴⁴⁻⁴⁶ Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin,⁴⁷ adenosine⁴⁸ and orexin,⁴⁹ but also reduce inflammation through dopamine.⁵⁰ On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia.51,52 If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke.53

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, 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, and 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 minimize confounders. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints. Further clinical trials with standardized acupoints should be conducted based on the findings of this

1		
3		
4 5	1	study.
6 7	2	
8 9	3	
10 11	4	
12 13	5	
14 15 16	6	
17 18	7	
19 20	8	
21 22 23	9	
23 24 25	10	
26 27	11	
28 29 20	12	
30 31 32	13	
33 34	14	
35 36	15	
37 38 39	16	
40 41	17	
42 43	18	
44 45	19	
46 47 48	20	
49 50	21	
51 52	22	
53 54	23	
55 56 57	24	
58 59	25	
60	26	16

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Conclusions

Our study demonstrates that the ischemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. It also offers important ideas <text> for more comprehensive studies in the future.

1 Acknowledgement

This study was based in part on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

9 Competing interests

10 The authors declare that they have no conflicts of interest.

12 Authors' contributions

CYH and MCH contributed equally. MCH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to 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 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 conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as co-corresponding authors.

24 Data availability

25 The datasets generated during and/or analysed during the current study are available

26 from the corresponding author on reasonable request.

References

- Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990; 16:513-37.
- Sesin CA, Bingham CO, 3rd. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2005;35:185-196.
- 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 Jun* 2008;15:762-784.
 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;69:1010-1014.
- 5. Smolen JS, Landewe 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;69:964-975.
- 6. Avina-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;59:1690-1697.
- 7. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular

BMJ Open

events in patients with rheumatoid arthritis: a meta-analysis of observational studies.
Ann Rheum Dis 2012;71:1524-1529.
8. de Groot L, Posthumus MD, Kallenberg CG, et al. Risk factors and early detection
of atherosclerosis in rheumatoid arthritis. Eur J Clin Invest 2010;40:835-842.
9. Meune C, Touze E, Trinquart 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;103:253-261.
10. Peters MJ, Symmons DP, 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;69:325-331.
11. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best
Pract Res Clin Rheumatol 2011;25:469-483.
12. 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;59:1090-1096.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

13. 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;41:863-877.

- 14. 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;33:248-255
- 15. Lai CH, Lai MS, Lai KL, et al. Nationwide population-based epidemiologic study of rheumatoid arthritis in Taiwan. *Clin Exp Rheumatol* 2012;30:358-363.
- 16. Liou TH, Huang SW, Lin JW, 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* 20113;72:541-546.
- Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. *Curr Treat Options Neurol* 2015;17:356.
- 19. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591-2602.
- 20. Bowman SJ. Hematological manifestations of rheumatoid arthritis. *Scand J Rheumatol* 2002;31:251-259.
- 21. Seca S, Patricio M, Kirch S, et al. Effectiveness of Acupuncture on Pain,

3
4
5
6
7
, Q
0
9
10
11
12
13
14
15
16
17
18
19
20
21
27
∠∠ ??
23
24
25
26
27
28
29
30
31
32
33
34
35
36
50 27
3/
38
39
40
41
42
43
44
45
46
47
48
49
50
51
57
52 52
55 54
54
55
56
57
58
59
60

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.

- 22. Tam LS, Leung PC, Li TK, et al. Acupuncture in the treatment of rheumatoid arthritis: a double-blind controlled pilot study. *BMC Complement Altern Med* 2007;7:35.
- 23. 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;15:187-193.
- 24. Chou PC, Chu HY. Clinical Efficacy of Acupuncture on Rheumatoid Arthritis and Associated Mechanisms: A Systemic Review. *Evid Based Complement Alternat Med* 2018;8596918.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

25. Huang CY, Wu MY, Huang MC, 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;14:1-9.
26. Huang MC, Pai FT, Lin CC, 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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

3
4
5
6
0
/
8
9
10
11
12
13
14
15
16
10
17
18
19
20
21
22
23
23
24
25
26
27
28
29
30
31
32
33
31
24 27
35
36
37
38
39
40
41
42
<u>4</u> 2
43
44
45
46
47
48
49
50
51
52
52
52
54
55
56
57
58
59
60

1 2

> 27. Shih CC, Liao CC, Sun MF, et al. A Retrospective Cohort Study Comparing Stroke Recurrence Rate in Ischemic Stroke Patients With and Without Acupuncture Treatment. *Medicine (Baltimore)* 2015;94:e1572.

> 28. Huang CY, Wu MY, Chang CL, 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;63:1-9.

29. Huang CY, Wu MY, Kuo YH, 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.

30. Wu MY, Huang MC, Liao HH, 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.

31.Wu MY, Lee YC, Lin CL, 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.

32. 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*

2	
3	
4	2017;76:17-28.
5	
6	
7	33 Karpouzas GA Ormseth SR Hernandez E et al Impact of Cumulative
8	
9	
10	Inflammation Cardiac Risk Factors and Medication Exposure on Coronary
11	initialinitation, Cardiae Nisk I actors, and Wedleation Exposure on Coronary
12	
13	Athorogalarogic Prograssian in Phaymatoid Arthritic Arthritic Phaymatol
14	Autoroscierosis Progression in Kileumatolu Artinitus. Artinitus Kileumator
15	
16	2020.72.400 409
17	2020;72:400-408.
18	
10	
20	34. Visvanathan S, Rahman MU, Keystone E, et al. Association of serum markers
20	
21	
22	with improvement in clinical response measures after treatment with golimumab in
23	
24	
25	patients with active rheumatoid arthritis despite receiving methotrexate: results
26	
27	
28	from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.
29	
30	
31	35 Kleinert S Tony HP Krause A et al Impact of national disease characteristics
32	set filometes, fong fil, filouse fi, et un impact of panent and abouse enalacteristics
33	
34	on the range tic success during adaligning treatment of natients with rheumatoid
35	on therapeutie success during adaminantab treatment of patients with meanatola
36	
37	arthritic: data from a German noninterventional observational study. <i>Phaumatal Int</i>
38	artifittis. data from a Ociman nominer ventional observational study. <i>Kneumuloi mi</i>
39	
40	2012.22.2750.2767
41	2012,52.2759-2767.
42	
42	
45	36. Wijbrandts CA, Dijkgraaf MG, Kraan MC, et al. The clinical response to
44	
45	
40	infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour
47	
48	
49	necrosis factor alpha expression in the synovium. Ann Rheum Dis
50	
51	
52	2008;67:1139-1144.
53	
54	
55	37. Karpouzas GA, Ormseth SR, Hernandez E, et al. Biologics may prevent
56	1 ····································
57	
58	cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque
59	carate rassular events in meanatora arannas by minorang coronary plaque
60	
	24

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

formation and stabilizing high-risk lesions. *Arthritis Rheumatol* 2020;72, 1467-1475.

- 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;177:508-515.
 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;179:1388-1397.

- 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;27:103-105.
- 42. Lee H, Lee JY, Kim YJ, et al. Acupuncture for symptom management of rheumatoid arthritis: a pilot study. *Clin Rheumatol* 2008;27:641-645.
- 43. Ouyang BS, Gao J, Che JL, 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;17:505-509.
 44. He X, Huang L, Qiu S, et al. beta-Endorphin attenuates collagen-induced arthritis

BMJ Open

partially by inhibiting peripheral pro-inflammatory mediators. Exp Ther Med
2018;15:4014-4018.
45. Ye TS, Du ZH, Li ZH, et al. Repeated Electroacupuncture Persistently Elevates
Adenosine and Ameliorates Collagen-Induced Arthritis in Rats. Evid Based
Complement Alternat Med 2016;3632168.
46. Li J, Li J, Chen R, et al. Targeting NF-kappaBeta 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;13:883-888.
49. Chen YH, Lee HJ, Lee MT, et al. Median nerve stimulation induces analgesia via
orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. Proc
<i>Natl Acad Sci U S A</i> 2018;115:E10720-E9.
50. Torres-Rosas R, Yehia G, Pena G, et al. Dopamine mediates vagal modulation of
the immune system by electroacupuncture. Nat Med 2014;20:291-295.
51. Hsieh CH. The effects of auricular acupressure on weight loss and serum lipid
levels in overweight adolescents. Am J Chin Med 2010;38:675-682.
26

2	
3	
4	52 Flachskampf FA Gallasch I Gefeller O et al Randomized trial of acupuncture to
5	
6	
7	lower blood pressure <i>Circulation</i> 2007:115:3121-3129
8	
9	
10	53. Semb AG. Ikdahl E. Wibetoe G. et al. Atherosclerotic cardiovascular disease
11	
12	
13	prevention in rheumatoid arthritis. Nat Rev Rheumatol 2020;16: 361-379.
14	1 ,
15	
16	
17	
18	
19	
20	
∠ I >>	
22 23	
25	
24	
25	
20	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
5/	
58	
59	
UO	
	27

	G4 1 1.						
X7 · 11	Ac	Acupuncture treatment					
variable	No (n =	= 11613)	Yes (n =	11613)	mean		
	n	%	n	%	unierence		
Sex							
Women	9499	81.8	9478	81.6	0.01		
Men	2114	18.2	2135	18.4	0.01		
Age group							
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 \pm 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		
Hyperlipidemia	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		

4:. whather T-1-1 1 01 £ ..1 : 1 +ŀ y

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Cyclosporine	555	4 78	544	4 68	0 004
Biological DMARDs	200	1.70	211	1.00	0.001
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid					
arthritis diagnosis and index,	(1078.52	2, 795.0)	(1065.18	, 707.0)	0.32
days (mean, median)					
Acupuncture visits (mean,		-	(9.83,	3.00)	
median)					

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD

(disease-modifying antirheumatic drugs).

3			open-				
Table 2. Subhazard ratios rheumatoid arthritis patients	and 95% costs using the co	onfidence	e intervals of ischemic str risks regression models.	oke associated	l with acupt	2023-075218 on 13 Reatment and of the second	covariat
1	No. of	1 0	Crude*			Adjusted [†]	
Variable	event (n = 946)	SHR	(95% CI)	p-value	SHR	den en source and the	p-
Acupuncture treatment		Ur				nloa uperi	
No	605	1.00	reference		1.00	d e d de reference	
Yes	341	0.52	(0.46, 0.60)	< 0.001	0.57	a A for (0.49, 0.65)	<
Sex						ES)	
Women	714	1.00	reference		1.00	≥ reference	
Men	231	1.44	(1.24, 1.67)	< 0.001	1.32	Tai b (1.14, 1.54)	<
Age group						ning	
18-39	13	1.00	reference		1.00	reference	
40-59	372	7.17	(4.14, 12.4)	< 0.001	5.99	sin (3.44, 10.4)	<
≥ 60	561	28.1	(16.3, 48.6)	< 0.001	14.7	a (8.38, 25.7)	<
Baseline Comorbidity						June	
(ref = no comorbidity)						nolo	
Diabetes mellitus	334	2.64	(2.31, 3.01)	< 0.001	1.58	gie 202 (1.36, 1.82)	<
Hypertension	654	3.96	(3.45, 4.54)	< 0.001	2.10	a (1.79, 2.47)	<
Hyperlipidemia	371	1.94	(1.70, 2.21)	< 0.001	1.08	b (0.93, 1.25)	
Congestive heart failure	148	3.18	(2.67, 3.79)	< 0.001	1.31	ີ ຍິ ເສີ. (1.08, 1.59)	C
						bliogr	
			30			aphiq	
	F	or peer re	view only - http://bmjopen.bmj.	com/site/about/	guidelines.xht	ml de	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

						X H	
						ı-2023- >pyrigt	
						-075218	
Depression	120	1.46	(1.21, 1.77)	< 0.001	1.12	uding 1, (0.91, 1.37)	0.2
Anxiety	256	1.40	(1.21, 1.61)	< 0.001	0.99	for Fer (0.85, 1.16)	0.9
Alcoholism	20	1.48	(0.95, 2.29)	0.08	1.46	s Enga (0.88, 2.43)	0.1
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32	ר פיק (0.07, 1.40) אַר (0.07, 1.40)	0.1
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10	te m	0.7
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89	te sw (0.66, 1.19)	0.4
Drugs used						nloa xt ar	
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51	a ieu (0.42-0.62)	< 0.0
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24	a for (0.11-0.51)	0.00
Statin	329	1.04	(0.92-1.17)	0.5575	0.65	(0.58-0.74)	< 0.0
Conventional DMARDS						9, A	
Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001	0.70	Taj (0.60, 0.81)	<0.0
Sulfasalazine	235	0.47	(0.41, 0.54)	< 0.001	0.80	(0.68, 0.94)	0.00
Methotrexate	2	1.88	(0.50, 7.04)	0.35	3.15	an (0.84, 11.9)	0.0
Leflunomide	18	0.22	(0.14, 0.35)	< 0.001	0.34	a gi (0.22, 0.54)	<0.0
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	1.07	niar 9 (0.61, 1.88)	0.0
Azathioprine	9	0.39	(0.20, 0.75)	0.004	0.77	ec un (0.40, 1.49)	0.4
Mycophenolate	0	-	-		-	e 11,	
Cyclosporine	35	0.62	(0.44, 0.87)	0.005	1.40	Gei 22 (0.99, 1.98)	0.0
Biological DMARDs						s. 5 at	
Etanercept	16	0.27	(0.16, 0.44)	< 0.001	0.51	B (0.31, 0.83)	0.00
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0.43	nce (0.14, 1.34)	0.1
Conventional DMARDS						Biblio	
			31			ıgraphi	

 Page 32 of 43

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 33 of 43				BMJ Oper	1	l by copy	njopen-2	
1 2 3 4	Hudrovyahloroquino	222	0.47	(0.41.0.54)	~0.001	rright, includin	0.23-075218 on	<0.001
5 6	Hydroxychioroquine	333	0.47	(0.41, 0.34)	<0.001	<u>0.70</u> o	$\frac{3}{\omega}$ (0.00, 0.81)	<0.001
7 8 9	Adjusted SHR ⁺ represents the	relative subhather he adjusted sub	zard ratio; bhazard rati	o: mutually adjusted for	accepted acupur	icture, age, 88	kacomorbidities, a	nd drugs used in
10	competing-risks regression	models.				elate	20	
11 12	Abbreviation: Nonsteroidal	l anti-inflamma	atory drugs	(NSAIDs), DMARD (d	isease-modifying	antirheumatiz	ärugs).	
12						o tex	No Million	
14						t an	nloa	
15 16						d da	ded	
17						(Ab ata r	fro	
18						ninii		
19 20						ng, .	tp://	
21						Altr	bm.	
22						aini	ope	
23 24						ing,	ň.b	
24						and	, mj.	
26						- I sin	ŏ	
27						nila	on	
28 29						r tec	Jur	
30						chno	не 1	
31						olog	1, 21	
32 33						ies.	025	
34							at A	
35							vger	
36 37							ICe	
38							Bibl	
39							liog	
40				32			rapl	
41 42				52			upir	
43		Ea	r neer review	only-http://hmiopen.hmi	com/site/about/au	delines vhtml	ē	
44		FC	n heel leview	omy - mup.// omjopen.omj.	com/site/about/gui	uennes.XIItinn	<u>e</u>	
45 46								
40								

BMJ Open Table 3. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritise patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and drug used using the competing-rise receives acupation of the stratification of sex, age, comorbidities and drug used using the competing-rise receives acupation of the stratification of sex, age, comorbidities and drug used using the competing-rise receives acupation of the stratification of sex, age, comorbidities and drug used using the competing-rise receives acupation of sex.

Variables			Rheum	atoid arth	Congressed with non-acupuncture users					
		No			Yes		E autle SHR	Adjusted SHR		
	(n = 11613)				(n = 11613)		bown of tex			
	Event	Person years	IR†	Event	Person years	IR [†]		(95% CI)		
			\mathcal{O}_{K}				ed frc ur (A data			
Total	605	48836	12.4	341	57273	5.95	0.52(1 4 5 0 .60)***	0.57(0.50, 0.65)***		
Sex							ng, .			
Women	460	40274	11.4	254	46907	5.41	$0.51(0_{4}^{2}44\frac{3}{2}0.60)^{***}$	0.58(0.49, 0.67)***		
Men	145	8562	16.9	87	10366	8.39	0.54(() 42 2 0.71)***	0.54(0.41, 0.70)***		
Age group							19, a			
18-39	5	8734	0.57	8	8576	0.93	1.47(0,49,49,4.45)	1.45(0.44, 4.76)		
40-59	226	29529	7.65	146	37225	3.92	0.53(0243 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							ne 1. chnc			
Diabetes mellitus							1, 20 logi			
No	383	41083	9.32	229	48060	4.76	0.55(0.47 ^b 0.65)***	0.60(0.51, 0.71)***		
Yes	222	7753	28.6	112	9213	12.2	0.47(0.38 20.59)***	0.52(0.41, 0.65)***		
Hypertension							ence			
No	184	32174	5.72	108	37634	2.87	0.52(0.41 - 0.66)***	0.57(0.45, 0.72)***		
							liog			
					33		raph			
							iique			
		For peer re	view only	- http://bmjo	ppen.bmj.com/site/a	bout/guidel	lines.xhtml			
Page 35 of 43		BMJ Open Spy -22								
------------------	------------------	------------------	----------	---------------	--------------	-------------------	---------------	--------------------------------------	---------------------	--
1 2 3 4								23-075218 c right, includ		
5	Yes	421	16661	25.3	233	19639	11.9	0.53(6 ,45,0.62)***	0.57(0.49, 0.67)***	
6 7	Hyperlipidemia							3 Fel		
8	No	366	36970	9.90	209	43496	4.81	0.53(8 45 <u>5</u> 0.62)***	0.61(0.51, 0.72)***	
9 10	Yes	239	11866	20.1	132	13777	9.58	0.51((20.63)***	0.51(0.41, 0.63)***	
11	Congestive heart							024. ted t		
12 13	failure							to te		
14	No	513	46595	11.0	285	54590	5.22	0.51() 4 4 0 0.59)***	0.55(0.47, 0.64)***	
15 16	Yes	92	2241	41.1	56	2683	20.9	0.61(04480.85)***	0.65(0.47, 0.92)***	
17	Depression							fror (AB		
18 10	No	523	44638	11.7	303	52396	5.78	0.54(E 4 2: 0.62)***	0.59(0.51, 0.67)***	
20	Yes	82	4198	19.5	38	4877	7.79	0.43(0 →30 ≥ 0.64)***	0.48(0.32, 0.72)***	
21 22	Anxiety							,l tra		
22	No	442	38718	11.4	248	46073	5.38	0.51(() 44, 0.60)***	0.56(0.48, 0.66)***	
24	Yes	163	10117	16.1	93	11200	8.30	0.55(0 43 0.71)***	0.57(0.44, 0.74)***	
25	Alcoholism							ùd si		
27 28	No	596	48177	12.4	330	56529	5.84	0.51(4 45 9 0.59)***	0.56(0.49, 0.64)***	
28	Yes	9	659	13.7	11	744	14.8	1.82(6.47, 2.67)	1.25(0.50, 3.09)	
30 21	Tobacco use							hnol		
32	No	603	48655	12.4	341	57090	5.97	0.52(6460.60)***	0.57(0.50, 0.65)***	
33 24	Yes	2	181	11.1	0	182	0.00	S. 15 at		
34 35	Obesity							Age		
36	No	598	48412	12.4	338	56737	5.96	0.52(0.46,0.60)***	0.57(0.50, 0.65)***	
37	Yes	7	424	16.5	3	536	5.60	0.38(0.1051.49)	0.40(0.14, 1.19)	
39								liogr		
40 41						34		aphi		
42								ique		
43 44			For peer	review only -	http://bmjop	pen.bmj.com/site/	/about/guidel	ines.xhtml		

				B	MJ Open		njopen-2023-075218 (1 by copyright, incluc		Page 36 o
Atrial fibrillation							on 1: ding		
No	576	46291	12.4	320	54553	5.87	0.51(0 2 45 5 0.59)***	0.56(0.49, 0.64)***	
Yes	29	2545	11.4	21	2720	7.72	0.72((8 4) <u>5</u> 1.26)	0.70(0.38, 1.30)	
Drugs used							ry 20 relat		
Oral steroid)24. eme ted t		
No	318	17828	17.8	166	21844	7.60	0.48(0,000,000,000,000,000,000,000,000,000,	0.53(0.44, 0.64)***	
Yes	287	31008	9.26	175	35429	4.94	0.56() $\hat{\mathbf{G}}_{\mathbf{A}}$ $\hat{\mathbf{G}}_{\mathbf{O}}$	0.59(0.49, 0.72)***	
NSAID							ded d da		
No	216	7329	29.5	105	9509	11.0	0.46(() 2 2 2 0.58)***	0.54(0.43, 0.69)***	
Yes	389	41506	9.37	236	47764	4.94	0.55((54)	0.56(0.48, 0.66)***	
Statin							р://b g, АI		
No	586	45820	12.8	322	54040	5.96	0.51((1)440.58)***	0.56(0.49, 0.64)***	
Yes	19	3016	6.30	19	3233	5.88	0.94((5 50) 1.79)	0.97(0.49, 1.95)	
Conventional DMARDS					C	2	omj.com/ , and sim		-
No	347	14099	24.6	181	18431	9.82	0.48(140,0.57)***	0.54(0.45, 0.65)***	-
Yes	258	34736	7.43	160	38842	4.12	0.56(64650.68)***	0.58(0.47, 0.71)***	-
Biological DMARDs							nolo		-
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-msks regression models. ibliographique de l

Page 37 of 43	BMJ Open S	njopen-2
1 2 3 4 5 6 7 8 9 10	*: p < 0.05; **: p < 0.01; *** p < 0.001 Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic	023-075218 on 13 rubruary 20
11 12 13 14 15 16 17	ed to text and data r	24. Downloaded from
18 19 20 21 22 23 24	nining, Al training,	n http://bmjopen.br
25 26 27 28 29 30	and similar techno	nj.com/ on June 11
31 32 33 34 35 36 37	logies.	, 2025 at Agence B
38 39 40 41 42 43	36 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	ibliographique de
44 45 46		_

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis 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.

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





Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



3		Rheumatoi				
+ 5 • • • • •		Accepted a	cupuncture			
5 Variable	No (n =	=22218)	Yes (n =	=12266)	difference	
3	n	%	n	%	_	
Gender						
11 Women	16702	75.2	10109	82.4	0.18	
12 13 Men	5516	24.8	2157	17.6	0.18	
Age group					-	
16 18-39	2994	13.5	1767	14.4	0.03	
40-59	12351	55.6	7762	63.3	0.16	
$ _{19}^{18} \ge 60$	6873	30.9	2737	22.3	0.20	
²⁰ Mean±SD (years)	56.7=	±14.7	54.3±	13.3	0.17	
Baseline Comorbidity					<u> </u>	
²³ Diabetes mellitus	4117	18.5	2260	18.4	0.003	
²⁴ ₂₅ Hypertension	8857	39.9	4632	37.8	0.04	
²⁶ Hyperlipidemia	5610	25.3	3593	29.3	0.09	
27 28 Congestive heart failure	1698	7.64	736	6.00	0.07	
²⁹ Depression	1901	8.56	1394	11.4	0.09	
Anxiety	4591	20.7	3118	25.4	0.11	
³² Alcoholism	422	1.90	244	1.99	0.01	
³³ 34 Tobacco used	146	0.66	84	0.68	0.003	
³⁵ Obesity	188	0.85	163	1.33	0.05	
Atrial fibrillation	1102	4.96	845	6.89	0.08	
³ Drug used						
10 Oral steroid	10814	48.7	6946	56.6	0.16	
¹¹ NSAID	13907	62.6	9532	77.7	0.34	
¹² 13 Statin	828	3.73	688	5.61	0.09	
Conventional DMARDS						
45 46 Hydroxychloroquine	9299	41.9	6059	49.4	0.15	
⁴⁷ Sulfasalazine	7210	32.5	4606	37.6	0.11	
18 19 Methotrexate	14	0.06	11	0.09	0.01	
Leflunomide	1309	5.89	973	7.93	0.08	
52 D-penicillamine	196	0.88	138	1.13	0.02	
Azathioprine	385	1.73	229	1.87	0.01	
55 Mycophenolate	10	0.05	7	0.06	0.01	
⁵⁶ Cyclosporine	816	3.67	594	4.84	0.06	
57 Biological DMARDs		2.07	- / -			
59 Etanercept	941	4.24	706	5.76	0.07	
50P	<i>/</i> · · ·		,	2.70	0.07	

 $\frac{1}{2}$ Supplement Table 1. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching.

	BMJ Oper	า			Page 42 of 43
Adalimumab	345	1.55	202	1.65	0.01
¹ Types of acupuncture					
3 Manual acupuncture			10604	86.45	
⁴ Electroacupuncture			407	3.32	
6 Combination of manual acupuncture and			1255	10.22	
⁷ electroacupuncture		125		10.25	
9Duration between rheumatoid arthritis date	(081.20	668 0)	(1047.24	(600 5)	
¹⁰ and index, days (mean, median)	(901.29,	008.0)	(1047.30	, 000.3)	
Acupuncture visits, (mean, meidan)			(10.43	, 3.00)	

¹³The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared Protected by copyright, includir 1sohort.

¹⁶Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs)

2Supplement Table 2. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted $\frac{22}{23}$ acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in 24in-matching.

2 <u>5</u> 26	X7 • 11	No. of event		Crude*			Adjusted [†]	ding
27	Variable	(n=1441)	SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
2 8 29 Ac	cepted acupuncture							Ses
30 N	No	1080	1.00	reference		1.00	reference	relat
31 32	Yes	361	0.48	(0.42, 0.53)	< 0.001	0.65	(0.58, 0.74)	<0.001
33 34Cru	ude SHR* represente	ed relative subhaza	rd ratio;	4				b text a
³⁵ Ad	justed SHR [†] represen	ted adjusted subha	zard ratio	: mutually adjust	ed for accept	ed acupund	cture, age, gend	er, and
30 30011	norbidities, and drug	s used in competin	g-risks reg	gression models.				data
38		-						- m
39								nin
40								g, /
41 42								
42 42								rain
+3 ΔΔ								ling
45								j, a
46								nd
47								sim
48								lla
49								r te
50								ĉh
51								nol
52								ogi
53								les

Page 43 of 43

	ST	'ROBE 2007 (v4) Statement—Checklist of items that should be included in reports of chase a control studies	
Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(b) Provide in the abstract an informative and balanced summary of what was done and what a short and what because the stract and the stract and balanced summary of what was done and what because the stract and the stract and the stract and balanced summary of what was done and what because the stract and the stract and balanced summary of what was done and what because the stract and the stract and balanced summary of what was done and what because the stract and th	1-5
Introduction		2022 Inter	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods		an de rieiei	
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and contropselection. Give the rationale for the choice of cases and controls	9-10
		(b) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier diagnostic criteria, if	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how matching of cases and controls was addressed	11
		(e) Describe any sensitivity analyses	11
Results		Ŭ a	

 lographique de l

		BMJ Open by copyrig copyrig 2023	Page 44
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information စာကုန်စုံosures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their predstary (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningfu	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses B	13
Discussion		ning S) t	
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of a alyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information		ar on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine 🕉 rg/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.sepidem.com/).

BMJ Open

Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-075218.R1
Article Type:	Original research
Date Submitted by the Author:	25-Sep-2023
Complete List of Authors:	Huang, Chia-Yu; China Medical University, Huang, Ming-Cheng; China Medical University Hospital, Department of Chinese Medicine Liao, Hou-Hsun; China Medical University Lin, Cheng-Li; China Medical University Hospital; China Medical University Lee, Yu-Chen; China Medical University, Graduate Institute of Acupuncture Science; China Medical University Hospital, Acupuncture Department Zimmerman, Gregory; China Medical University Wu, Mei-Yao; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University
Primary Subject Heading :	Complementary medicine
Secondary Subject Heading:	Rheumatology, Neurology
Keywords:	Stroke < NEUROLOGY, COMPLEMENTARY MEDICINE, RHEUMATOLOGY

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1	Acupuncture decreased the risk of ischemic stroke in patients with
2	rheumatoid arthritis: a nationwide propensity score-matched study
3	
4	Authors:
5	Chia-Yu Huang, M.D., Ph.D. ^{1,2†} , Ming-Cheng Huang, M.D., Ph.D. ^{1,3†} , Hou-Hsun
6	Liao, M.D., M.S. ^{2,3} , Cheng-Li Lin, M.S. ^{4,5} , Yu-Chen Lee, M.D., Ph.D. ^{3,6} , Gregory
7	Zimmerman, M.S. ⁶ , Mei-Yao Wu, M.D., Ph.D. ^{3,7,8,††} , Hung-Rong Yen, M.D.,
8	Ph.D. ^{1,3,8,9,10,††}
9	[†] Chia-Yu Huang and Ming-Cheng Huang contributed equally to this work and share
10	first authorship.
11	[†] [†] Mei-Yao Wu and Hung-Rong Yen contributed equally to this work and share
12	corresponding authorship.
13	
14	Affiliations:
15	¹ Department of Family Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi
16	Medical Foundation, Taichung, Taiwan
17	² Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of
18	Chinese Medicine, China Medical University, Taichung, Taiwan
19	³ Department of Chinese Medicine, China Medical University Hospital, Taichung,
20	Taiwan
21	⁴ Management Office for Health Data, China Medical University Hospital, Taichung,
22	Taiwan.
23	⁵ College of Medicine, China Medical University, Taichung, Taiwan
24	⁶ Graduate Institute of Acupuncture Science, College of Chinese Medicine, China

BMJ Open

25 Medical University

1 2		
3 4	1	⁷ School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine,
5 6 7	2	China Medical University, Taichung, Taiwan
7 8 9	3	⁸ Research Center for Traditional Chinese Medicine, Department of Medical Research,
10 11	4	China Medical University Hospital, Taichung, Taiwan
12 13	5	⁹ Chinese Medicine Research Center, China Medical University, Taichung, Taiwan
14 15 16	6	
10 17 18	7	Corresponding authors:
19 20	8	Hung-Rong Yen, M.D., Ph.D.
21 22	9	School of Chinese Medicine, College of Chinese Medicine, China Medical University,
23 24 25	10	Taichung, Taiwan
25 26 27	11	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
28 29	12	Tel.: +886-4-22053366 ext. 3313
30 31	13	Fax: +886-4-22365141
32 33 24	14	E-mail: hungrongyen@gmail.com
35 36	15	or
37 38	16	Mei-Yao Wu, M.D., Ph.D.
39 40	17	School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, China
41 42 43	18	Medical University, Taichung, Taiwan
43 44 45	19	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
46 47	20	Tel.: +886-4-22052121 ext. 4561
48 49	21	Fax: +886-4-22365141
50 51 52	22	E-mail: meiyaowu0919@gmail.com
53 54	23	
55 56	24	E-mail addresses for all authors:
57 58	25	Chia-Yu Huang: dochuangcharlie@gmail.com
59 60	26	Ming-Cheng Huang: mchuang1128@gmail.com 2

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

2	
3 4 5	1
5 6 7	2
, 8 9	3
10 11	4
12 13	5
14 15	6
16 17	7
18 19 20	8
20 21 22	9
23 24	10
25 26	10
27 28	11
29 30	12
31 32	13
33 34	14
35 36	15
37 38	16
39 40	17
41 42	18
43 44 45	19
45 46 47	20
48 49	21
50 51	22
52 53	22
54 55	23
56 57	24
58 59	25
60	26

Hou-Hsun Liao: a202098@cmu.edu.tw

Cheng-Li Lin: orangechengli@gmail.com

Yu-Chen Lee: d5167@mail.cmuh.org.tw

Gregory Zimmerman: gregzlac@gmail.com

Mei-Yao Wu: meiyaowu0919@gmail.com

Hung-Rong Yen: hungrongyen@mail.cmu.edu.tw

Research Database; Rheumatoid arthritis; Stroke.

Running title: Acupuncture Reduced the Risk of Stroke

Word count: Abstract: 275; Text: 2490; No of Tables: 1; No of Figures: 2

Keywords: Acupuncture; Cardiovascular diseases; National Health Insurance

1 2		
2 3 4	1	Abstract
5 6 7	2	Objectives: The purpose of this study was to demonstrate that acupuncture is
8 9	3	beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid
10 11	4	arthritis (RA).
12 13 14	5	Design: This is a propensity score-matched cohort study.
15 16	6	Setting: This is a nationwide population-based study.
17 18	7	Participants: The patients with RA diagnosed between 1 January 1997 and 31
19 20	8	December 2010 through the National Health Insurance Research Database.
21 22 23	9	Interventions: The patients who were administered acupuncture therapy from the
24 25	10	initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were
26 27	11	included in the acupuncture cohort. Patients who did not receive acupuncture
28 29	12	treatment during the same time interval were regarded as the no-acupuncture cohort.
30 31 32	13	Primary outcome measures: A Cox regression model was used to adjust for age, sex,
33 34	14	comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of
35 36	15	IS between these two cohorts through competing-risks regression models.
37 38	16	Results: After a 1:1 propensity score match, a total of 23,226 patients were identified.
39 40 41	17	The basic characteristics of these patients were similar. A lower cumulative incidence
42 43	18	of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$;
44 45	19	immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the end, 341
46 47 48	20	patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in
40 49 50	21	the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic
51 52	22	stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic
53 54	23	stroke incidence through acupuncture therapy in RA patients was independent of sex,
55 56 57	24	age, types of drugs used, and comorbidities.
57 58 59	25	Conclusions: This study showed the beneficial effect of acupuncture in reducing the
60	26	incidence rate of ischemic stroke in patients with RA.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

2	
3 4	
5	
6 7	
8	
9 10	
10	
12	
13 14	
15	
16 17	
18	
19 20	
21	
22 23	
24	1
25 26	
27	-
28 29	-
30 21	
32	-
33 34	-
35	
36 37	-
38	-
39 40	
41	
42 43	-
44	-
45 46	
47	4
48 49	2
50	
52	4
53	2
55	-
56 57	4
58	2
59 60	
00	4

2

4

5

1 Strengths and limitations of this study:

• Our research disclose the possible long-term effect from acupuncture in stroke

3 prevention which could not be investigated from clinical trial.

• Lower ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.

• The causality could not be proved directly as clinical trial through our study design.

7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	5
	5

1 Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness [1]. The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD) [2-5]. Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke [6-11]. Comparing to general population, stroke is more common noted in the RA patients [12]. The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively [13-15]. But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue to clinical doctors and patients [18]. The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF- α inhibitor) and anakinra (IL-1 inhibitor) [3,5,19]. And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients [18]. But some of them could bring the complications in the bone marrow to cause thrombocytopenia [20]. The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA [21-25]. A previous cohort

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

study founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture [26]. Furthermore, secondary stroke prevention is also noted from acupuncture therapy in the Taiwanese [27]. And the hypothesis in the acupuncture to lower stroke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population [28]. In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database [29]. We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

Materials and Methods

2 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. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or 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 a 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 (CMUH104-REC2-115).

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

21 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 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA 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 minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient 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 no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

17 Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and \geq 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401-405), hyperlipidemia (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,

BMJ Open

2	
3	
4	
5	
6	
7	
/	
8	
9	
10	
11	
12	
13	
14	
15	
10	
10	
17	
18	
19	
20	
21	
22	
23	
2J 2∕I	
24	
25	
26	
27	
28	
29	
30	
31	
32	
22	
ע גר	
24	
35	
36	
37	
38	
39	
40	
41	
42	
43	
11	
44	
4) 42	
46	
47	
48	
49	
50	
51	
52	
53	
51	
55	
22	
50	
57	
58	
59	
60	

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 ischemic
 stroke (ICD-9-CM: 433-438) were compared between acupuncture and
 non-acupuncture cohort of RA patients.

5

6 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

11

12 Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline 13 14 characteristics of the acupuncture and no-acupuncture cohorts as previously described 15 [30]. A negligible difference in mean values or proportions between the two cohorts 16 was defined as less than 0.1 standard deviation (SD). A competing-risks regression 17 models was performed to estimate the crude and adjusted subhazard ratios (SHRs) of 18 acupuncture therapy, age, sex, comorbidities, and types of drugs used. The 19 Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 20 21 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical 22 Computing, Vienna, Austria) to perform statistical analyses and create the figures. 23 Statistical significance was defined as p < 0.05 in two-tailed tests.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

24

25 Patient and Public Involvement

26 None

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (Fig. 1). The baseline characteristics of both cohorts are presented in Table 1, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% 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, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (Supplementary Table 1). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

BMJ Open

cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, p < 0.001, **Fig. 2**).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50-0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95%) CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥ 40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44-0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in **Supplementary Table 3** and **4**. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the 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 ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA [32]. Inflammation is a consistent and independent predictor of CVD in RA [33]. TNF- α is a cytokine that mediates inflammation 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 CVD risk in RA [37]. Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

There are a couple evidences and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the amounts 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 the RA patients, acupuncture was found to reduce TNF-a and vascular endothelial growth factor to improve the inflammation of RA [43]. In

animal studies, acupuncture reduced inflammation in collagen-induced arthritis model [44-46]. Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin [47], adenosine [48] and orexin [49], but also reduce inflammation through dopamine [50]. On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [51,52]. If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke [53].

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, 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 minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. And the algorithm for risk to develop cardiovascular events, such as the Framingham Risk Score is hard to form, because of lacking the above information. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (Supplementary Fig. 1) [55,56]. Further clinical trials with standardized acupoints should be conducted based on the findings of this study. And the difference of treatment results among various types of interventions could not be found from our database which did not belong to our result measure. The evidence of treatment dose of acupuncture therapy is still establishing, scurs the to₁. thus we did not discuss the topic in here.

1 2		
3	1	Conclusions
5 6 7	2	Our study demonstrates that the ischemic stroke risk could be reduced by
7 8 9	3	acupuncture treatment in patients with RA in Taiwan. It also offers important ideas
10 11	4	for more comprehensive studies in the future.
12 13	5	
14 15	6	
16 17	7	
18 19	, Q	
20 21	0	
22 23	9	
24 25	10	
26 27	11	
28 29	12	
30 31	13	
32 33 34	14	
35 36	15	
37 38	16	
39 40	17	
41 42	18	
43 44	19	
45 46	20	
47 48	20	
49 50	21	
51 52	22	
53 54	23	
55 56 57	24	
57 58 50	25	
60	26	
		10

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ethics Approval Statement

The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Competing Interests: 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.

Funding

This work was financially supported by the "Chinese Medicine Research Center, China Medical University" from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-1). This study was also supported in part by China Medical University (CMU103-BC-4-2, CMU105-BC-1-1, CMU105-BC-1-2), China Medical University Hospital (DMR-107-011, DMR-110-002, and DMR-111-105), and Ministry of Science and Technology (MOST108-2638-B-039-001-MY2, MOST107-2320-B-039-037, MOST108-2320-B-039-021, and MOST110-2321-B-

039-003). This study is also supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW111-TDU-B-212-134004), Taiwan. None of the funders and institutions listed had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgement

This study was based in part on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of

Health and Welfare, and managed by National Health Research Institutes. The
 interpretation and conclusions contained herein do not represent those of National
 Health Insurance Administration, Ministry of Health and Welfare, or National Health
 Research Institutes.

to occurrent on the terms on the one of the terms on the one of the terms on the one of the one of

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1	References
2	1. Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am 1990;
3	16:513-37.
4	2. Sesin CA, Bingham CO, 3 rd . Remission in rheumatoid arthritis: wishful thinking or
5	clinical reality? Semin Arthritis Rheum 2005;35:185-196.
6	3. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008
7	recommendations for the use of nonbiologic and biologic disease-modifying
8	antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum Jun 2008;15:762-784.
9	4. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of
10	rheumatoid arthritis with glucocorticoids: a systematic literature review informing
11	the EULAR recommendations for the management of rheumatoid arthritis. Ann
12	<i>Rheum Dis</i> 2010;69:1010-1014.
13	5. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the
14	management of rheumatoid arthritis with synthetic and biological
15	disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-975.
16	6. Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality
17	in patients with rheumatoid arthritis: a meta-analysis of observational studies.
18	Arthritis Rheum 2008;59:1690-1697.
19	7. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular

Page 21 of 44

BMJ Open

ional studies.	-
y detection	-
5-842.	P
ar events in	rotected
d stroke	by copy
	right, in
	cluding
	Ens for uses
heumatoid	eigneme related
	nt Supe to text a
	rieur (AE nd data I
tis. <i>Best</i>	3ES) . nining, <i>F</i>
	l trainin
eumatologic,	g, and si
ritis: a	milar teo
	chnologi
aatoid	ēs.
into int	Ċ
	c

1	events in patients with rheumatoid arthritis: a meta-analysis of observational studies.
2	Ann Rheum Dis 2012;71:1524-1529.
3	8. de Groot L, Posthumus MD, Kallenberg CG, et al. Risk factors and early detection
4	of atherosclerosis in rheumatoid arthritis. Eur J Clin Invest 2010;40:835-842.
5	9. Meune C, Touze E, Trinquart L, et al. High risk of clinical cardiovascular events in
6	rheumatoid arthritis: Levels of associations of myocardial infarction and stroke
7	through a systematic review and meta-analysis. Arch Cardiovasc Dis
8	2010;103:253-261.
9	10. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based
10	recommendations for cardiovascular risk management in patients with rheumatoid
11	arthritis and other forms of inflammatory arthritis. Ann Rheum Dis
12	2010;69:325-331.
13	11. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best
14	Pract Res Clin Rheumatol 2011;25:469-483.
15	12. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic,
16	and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a
17	nested, case-control study. Arthritis Rheum 2008;59:1090-1096.
18	13. Almutairi K, Nossent J, Preen D, et al. The global prevalence of rheumatoid
19	arthritis: a meta-analysis based on a systematic review. Rheumatol Int

Page 22 of 44

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2
3
1
4 r
5
6
7
8
9
10
10
11
12
13
14
15
16
17
10
10
19
20
21
22
23
24
2- 1 2⊑
25
26
27
28
29
30
21
21
32
33
34
35
36
27
20
38
39
40
41
42
43
11
44
45
46
47
48
49
50
50
21
52
53
54
55
56
50
57
58
59
60

1

1	2021;41:863-877.
2	14. Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Patient, disease, and
3	therapy-related factors that influence discontinuation of disease-modifying
4	antirheumatic drugs: a population-based incidence cohort of patients with
5	rheumatoid arthritis. J Rheumatol 2006;33:248-255
6	15. Lai CH, Lai MS, Lai KL, et al. Nationwide population-based epidemiologic study
7	of rheumatoid arthritis in Taiwan. Clin Exp Rheumatol 2012;30:358-363.
8	16. Liou TH, Huang SW, Lin JW, et al. Risk of stroke in patients with rheumatism: a
9	nationwide longitudinal population-based study. Sci Rep 2014;4:5110.
10	17. Holmqvist M, Gränsmark E, Mantel A, et al. Occurrence and relative risk of
11	stroke in incident and prevalent contemporary rheumatoid arthritis. Ann Rheum Dis
12	20113;72:541-546.
13	18. Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. Curr Treat
14	<i>Options Neurol</i> 2015;17:356.
15	19. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med
16	2004;350:2591-2602.
17	20. Bowman SJ. Hematological manifestations of rheumatoid arthritis. Scand J
18	Rheumatol 2002;31:251-259.
19	21. Seca S, Patricio M, Kirch S, et al. Effectiveness of Acupuncture on Pain,

 BMJ Open

2		
3		
4	1	Functional Disability, and Quality of Life in Rheumatoid Arthritis of the Hand:
5		
6		
7	2	Results of a Double-Blind Randomized Clinical Trial. J Altern Complement Med
8		1
9		
10	3	2019;25:86-97.
11		
12		
13	4	22. Tam LS, Leung PC, Li TK, et al. Acupuncture in the treatment of rheumatoid
14		
15		
16	5	arthritis: a double-blind controlled pilot study. BMC Complement Altern Med
17		
18		
19	6	2007:7:35.
20		
21		
22	7	23. Bernateck M, Becker M, Schwake C, et al. Adjuvant auricular electroacupuncture
23		, , , , , , , , , , , , , , , , , , , ,
24		
25	8	and autogenic training in rheumatoid arthritis: a randomized controlled trial.
26		
27		
28	9	Auricular acupuncture and autogenic training in rheumatoid arthritis. <i>Forsch</i>
29		
30		
31	10	Komplementmed 2008;15:187-193.
32		1
33		
34	11	24. Chou PC, Chu HY. Clinical Efficacy of Acupuncture on Rheumatoid Arthritis and
35		
36		
37	12	Associated Mechanisms: A Systemic Review. Evid Based Complement Alternat
38		
39		
40	13	<i>Med</i> 2018;8596918.
41		
42		
43	14	25. Huang CY, Wu MY, Huang MC, et al. The Association Between Acupuncture
44		
45		
46	15	Therapies and Reduced Fracture Risk in Patients with Osteoarthritis: A Nationwide
4/		
48		
49	16	Retrospective Matched Cohort Study. J Integr Complement Med 2022;14:1-9.
50		
51		
5∠ 52	17	26. Huang MC, Pai FT, Lin CC, et al. Characteristics of traditional Chinese medicine
5 3		
54 55		
55 56	18	use in patients with rheumatoid arthritis in Taiwan: A nationwide population-based
50 57		
5/ 50		
50 50	19	study. J Ethnopharmacol 2015;176:9-16.
59 60		
00		

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Page 24 of 44

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2
3
4
5
6
7
, 8
0
9 10
10
11
12
13
14
15
16
17
18
19
20
21
ר ∠ בר
22
23
24
25
26
27
28
29
30
31
37
22
22
34
35
36
37
38
39
40
41
42
43
44
77 15
45
40
4/
48
49
50
51
52
53
54
55
56
57
57
20
59
60

1	27. Shih CC, Liao CC, Sun MF, et al. A Retrospective Cohort Study Comparing
2	Stroke Recurrence Rate in Ischemic Stroke Patients With and Without Acupuncture
3	Treatment. Medicine (Baltimore) 2015;94:e1572.
4	28. Huang CY, Wu MY, Chang CL, et al. Coprescription Trends in Western Medicine,
5	Chinese Herbal Medicine and Dental Medicine among Older Adults in Taiwan
6	from 1997 to 2013. Complement Ther Med 2021;63:1-9.
7	29. Huang CY, Wu MY, Kuo YH, et al. Chinese Herbal Medicine Is Helpful for
8	Survival Improvement in Patients With Multiple Myeloma in Taiwan: A
9	Nationwide Retrospective Matched-Cohort Study. Integr Cancer Ther
10	2020;19:1-10.
11	30. Wu MY, Huang MC, Liao HH, et al. Acupuncture decreased the risk of coronary
12	heart disease in patients with rheumatoid arthritis in Taiwan: a Nationwide
13	propensity score-matched study. BMC Complement Altern Med 2018;18:341.
14	31.Wu MY, Lee YC, Lin CL, et al. Trends in use of acupuncture among adults in
15	Taiwan from 2002 to 2011: A nationwide population-based study. PloS one
16	2018;13:e0195490.
17	32. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for
18	cardiovascular disease risk management in patients with rheumatoid arthritis and
19	other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis

BMJ Open

2		
3		
4	1	2017;76:17-28.
5		
7	h	22 Komenses CA Omnesth SD Hemender E stell Immest of Computative
8	Z	55. Karpouzas GA, Ormsetn SK, Hernandez E, et al. Impact of Cumulative
9		
10	3	Inflammation Cardiac Risk Factors and Medication Exposure on Coronary
11	5	initiation, Cardiae Risk Factors, and Medication Exposure on Coronary
12		
13	4	Atherosclerosis Progression in Rheumatoid Arthritis. Arthritis Rheumatol
14		
15		
10 17	5	2020;72:400-408.
17		
10	c	24 Viewenthan & Dahman MU Kayatana E at al Association of some markers
20	б	34. Visvanatinan S, Kanman MO, Keystone E, et al. Association of serum markers
21		
22	7	with improvement in clinical response measures after treatment with golimumah in
23	,	with improvement in enhibit response measures after treatment with gommaniae in
24		
25	8	patients with active rheumatoid arthritis despite receiving methotrexate: results
26		
27		
28	9	from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.
30		
31	10	25 Klainart S. Tany UD. Krausa A. at al Impact of nations and discass a characteristics
32	10	55. Kiement S, Tony IIF, Klause A, et al. Impact of patient and disease characteristics
33		
34	11	on therapeutic success during adalimumab treatment of patients with rheumatoid
35		
36		
3/	12	arthritis: data from a German noninterventional observational study. Rheumatol Int
38		
39 40	10	2012-22-2750 27/7
41	13	2012;32:2759-2767.
42		
43	14	36 Wijbrandts CA Dijkgraaf MG Kraan MC et al. The clinical response to
44	± .	50. Wijorundus eri, Dijkgruur We, Kruun We, et ul. The enniour response to
45		
46	15	infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour
47		
48	_	
49 50	16	necrosis factor alpha expression in the synovium. Ann Rheum Dis
51		
52	17	2008-67-1130-1144
53	17	2000;07:1139-1144.
54		
55	18	37. Karpouzas GA, Ormseth SR, Hernandez E, et al. Biologics may prevent
56		
57		
50 50	19	cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque
60		
		24
		24
Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1	formation and stabilizing high-risk lesions. Arthritis Rheumatol 2020;72,
2	1467-1475.
3	38. Bao T, Patil S, Chen C, et al. Effect of Acupuncture vs Sham Procedure on
4	Chemotherapy-Induced Peripheral Neuropathy Symptoms: A Randomized Clinical
5	Trial. JAMA Netw Open 2020;3:e200681.
6	39. Zhao L, Chen J, Li Y, et al. The Long-term Effect of Acupuncture for Migraine
7	Prophylaxis: A Randomized Clinical Trial. JAMA Intern Med 2017;177:508-515.
8	40. Zhao L, Li D, Zheng H, et al. Acupuncture as Adjunctive Therapy for Chronic
9	Stable Angina: A Randomized Clinical Trial. JAMA Intern Med
10	2019;179:1388-1397.
11	41. Wang R, Jiang C, Lei Z, et al. The role of different therapeutic courses in treating
12	47 cases of rheumatoid arthritis with acupuncture. J Tradit Chin Med
13	2007;27:103-105.
14	42. Lee H, Lee JY, Kim YJ, et al. Acupuncture for symptom management of
15	rheumatoid arthritis: a pilot study. Clin Rheumatol 2008;27:641-645.
16	43. Ouyang BS, Gao J, Che JL, et al. Effect of electro-acupuncture on tumor necrosis
17	factor-alpha and vascular endothelial growth factor in peripheral blood and joint
18	synovia of patients with rheumatoid arthritis. Chin J Integr Med 2011;17:505-509.
19	44. He X, Huang L, Qiu S, et al. beta-Endorphin attenuates collagen-induced arthritis

Page 27 of 44

BMJ Open

1	partially by inhibiting peripheral pro-inflammatory mediators. Exp Ther Med
2	2018;15:4014-4018.
3	45. Ye TS, Du ZH, Li ZH, et al. Repeated Electroacupuncture Persistently Elevates
4	Adenosine and Ameliorates Collagen-Induced Arthritis in Rats. Evid Based
5	Complement Alternat Med 2016;3632168.
6	46. Li J, Li J, Chen R, et al. Targeting NF-kappaBeta and TNF-alpha Activation by
7	Electroacupuncture to Suppress Collagen-induced Rheumatoid Arthritis in Model
8	Rats. Altern Ther Health Med 2015;21:26-34.
9	47. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of
10	different frequencies. Trends Neurosci 2003;26:17-22.
11	48. Goldman N, Chen M, Fujita T, et al. Adenosine A1 receptors mediate local
12	anti-nociceptive effects of acupuncture. Nat Neurosci 2010;13:883-888.
13	49. Chen YH, Lee HJ, Lee MT, et al. Median nerve stimulation induces analgesia via
14	orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. Proc
15	Natl Acad Sci U S A 2018;115:E10720-E9.
16	50. Torres-Rosas R, Yehia G, Pena G, et al. Dopamine mediates vagal modulation of
17	the immune system by electroacupuncture. Nat Med 2014;20:291-295.
18	51. Hsieh CH. The effects of auricular acupressure on weight loss and serum lipid
19	levels in overweight adolescents. Am J Chin Med 2010;38:675-682.

2	
3 4 5	1
6 7 8	2
9 10 11	3
12 13 14	4
15 16 17	5
18 19 20	6
21 22 23	7
23 24 25 26	8
20 27 28	9
29 30 31	10
32 33 34	11
35 36 37	12
38 39 40	
41 42 43	14
44 45 46	14
47 48 40	15
49 50 51	16
52 53 54	17
55 56 57	18
58 59 60	19

1	52. Flachskampf FA, Gallasch J, Gefeller O, et al. Randomized trial of acupuncture to
2	lower blood pressure. Circulation 2007;115:3121-3129.
3	53. Semb AG, Ikdahl E, Wibetoe G, et al. Atherosclerotic cardiovascular disease
4	prevention in rheumatoid arthritis. Nat Rev Rheumatol 2020;16:361-379.
5	54. Rassen JA, Shelat A.A, Myers J, et al. One-to-many propensity score matching in
6	cohort studies. Pharmacoepidemiol Drug Saf 2012;21:69-80.
7	55. Tou SI, Huang CY, Yen HR. Effect of Acupoint Stimulation on Controlling Pain
8	from Heel Lance in Neonates: A Systematic Review and Meta-Analysis of
9	Randomized Controlled Trials. Children 2023;10:1024.
LO	56. Lin JG, Li TM, Hsu SF. Newly Edited Color Book of Acupuncture and
11	Moxibustion; JYIN Publishing Company: Taipei, Taiwan, 2009.
12	
13	
L4	
15	
16	
L7	
18	
19	

1 Acknowledgement

This study was based in part on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

9 Competing interests

10 The authors declare that they have no conflicts of interest.

12 Authors' contributions

CYH and MCH contributed equally. MCH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to 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 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 conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as co-corresponding authors.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

24 Data availability

25 The datasets generated during and/or analysed during the current study are available

26 from the corresponding author on reasonable request.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
17	
14	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30 21	
21	
22	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
4/	
48	
49 50	
50	
57	
52	
54	
55	
56	
57	
58	
59	
60	

1

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

	heumate	oid Arthrit	S4					
X 7	Ac	Acupuncture treatment						
variable	No (n =	= 11613)	Yes (n =	11613)	mean d:fformer of			
	n	%	n	%	unterence			
Sex								
Women	9499	81.8	9478	81.6	0.01			
Men	2114	18.2	2135	18.4	0.01			
Age group								
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			
Hyperlipidemia	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			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Cyclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid					
arthritis diagnosis and index,	(1078.52	2, 795.0)	(1065.18, 707.0)		0.32
days (mean, median)					
Acupuncture visits (mean,		-	(9.83, 2	3.00)	
median)					

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD

(disease-modifying antirheumatic drugs).

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis 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.

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



Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.



Page 35 of 44

BMJ Open 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.

	No. of		Crude [*]		-075 1t, ir	Adjusted [†]	
Variable	event (n = 946)	SHR	(95% CI)	p-value	218 on 1 IcluR ng	(95% CI)	p-value
Acupuncture treatment					3 Fel for u		
No	605	1.00	reference		1 s b s	reference	
Yes	341	0.52	(0.46, 0.60)	< 0.001		(0.49, 0.65)	< 0.001
Sex					024. ted t		
Women	714	1.00	reference			reference	
Men	231	1.44	(1.24, 1.67)	< 0.001	1 ar log	(1.14, 1.54)	< 0.001
Age group					ided id da		
18-39	13	1.00	reference		1 \$ 0 8 g	reference	
40-59	372	7.17	(4.14, 12.4)	< 0.001		(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					l trai		
(ref = no comorbidity)					ining		
Diabetes mellitus	334	2.64	(2.31, 3.01)	< 0.001	1မ္ဘာ8 <mark>ည်</mark>	(1.36, 1.82)	< 0.001
Hypertension	654	3.96	(3.45, 4.54)	< 0.001	2 ឆ្នាំ 0 ទ្ឋິ	(1.79, 2.47)	< 0.001
Hyperlipidemia	371	1.94	(1.70, 2.21)	<0.001		(0.93, 1.25)	0.30
Congestive heart failure	148	3.18	(2.67, 3.79)	<0.001	1 <mark>ខ្ល</mark> ី1 រុ	(1.08, 1.59)	0.006
Depression	120	1.46	(1.21, 1.77)	< 0.001		(0.91, 1.37)	0.28
Anxiety	256	1.40	(1.21, 1.61)	< 0.001	000000000000000000000000000000000000000	(0.85, 1.16)	0.94
Alcoholism	20	1.48	(0.95, 2.29)	0.08	<u>ج</u> 1.46 ع	(0.88, 2.43)	0.14
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32 P	(0.07, 1.40)	0.13
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10 e	(0.58, 2.08)	0.77
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89 <mark>Bib</mark>	(0.66, 1.19)	0.43
Drugs used					iogra		
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51 b i	(0.42-0.62)	< 0.0001
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24 G	(0.11-0.51)	0.0002
Statin	329 For p	eer review 1.04	only - http://bmiopen.bmj.com/ (0.92-1.17)	/site/about/guidelines 0.5575	^{s.xhtml} .65 e	(0.58-0.74)	< 0.0001

Conventional DMARDS			BMJ Open		njopen- 1 by co		Page 36 of	f 44
Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001	0 <u>7</u> 7023	(0.60, 0.81)	< 0.001	
Sulfasalazine	235	0.47	(0.41, 0.54)	< 0.001	0 <u>18</u> 0 05	(0.68, 0.94)	0.007	
Methotrexate	2	1.88	(0.50, 7.04)	0.35	nc15218	(0.84, 11.9)	0.08	
Leflunomide	18	0.22	(0.14, 0.35)	< 0.001		(0.22, 0.54)	< 0.001	
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	ן ק07 ד	(0.61, 1.88)	0.05	
Azathioprine	9	0.39	(0.20, 0.75)	0.004		(0.40, 1.49)	0.44	
Mycophenolate	0	-	-		ary 2 seigr s rela	-		
Cyclosporine	35	0.62	(0.44, 0.87)	0.005		(0.99, 1.98)	0.06	
Biological DMARDs					Dov to te			
Etanercept	16	0.27	(0.16, 0.44)	< 0.001		(0.31, 0.83)	0.007	
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	(0.14, 1.34)	0.15	
Conventional DMARDS					l froi . (AE ata r			
Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001		(0.60, 0.81)	< 0.001	
				0	j.com/ on nd simila	5-7.		
					n June 1 ar techn			
					1, 2(olog			
)25 ز ies.			
					at Ag			
					Jenc			
					ë			
					blio			
					graț			
					ohiq			
	F							
	For	peer review only	- nttp://bmjopen.bmj.com	/site/about/guideline	es.xntmi			

Page 37 of 44

BMJ Open Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke britering rise umatoid 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			Rheum	atoid arthr	E Scompared with non-acupuncture users				
	No				Yes		Crude SHR	Adjusted SHR	
		(n = 11613)			(n = 11613)		on 1:		
	Event	Person years	\mathbf{IR}^{\dagger}	Event	Person years	\mathbf{IR}^{\dagger}	or Ef (95% CI)	(95% CI)	
Total	605	48836	12.4	341	57273	5.95	s seight and a seight and a seight and a seight and a seight a sei	0.57(0.50, 0.65)***	
Sex							d to		
Women	460	40274	11.4	254	46907	5.41	1 000000000000000000000000000000000000	0.58(0.49, 0.67)***	
Men	145	8562	16.9	87	10366	8.39	$a_{D} = \frac{1}{2} \frac{1}$	0.54(0.41, 0.70)***	
Age group							ed fr data		
18-39	5	8734	0.57	8	8576	0.93	and the second s	1.45(0.44, 4.76)	
40-59	226	29529	7.65	146	37225	3.92	0.5 5 (0.43, 0.66)***	0.54(0.44, 0.66)***	
≥ 60	374	10573	35.4	187	11472	16.3	₹0.5 (0.46, 0.65)***	0.58(0.48, 0.69)***	
Baseline Comorbidity							jope raini		
Diabetes mellitus							ng,		
No	383	41083	9.32	229	48060	4.76	a).55(0.47, 0.65)***	0.60(0.51, 0.71)***	
Yes	222	7753	28.6	112	9213	12.2	0.4 4 (0.38, 0.59)***	0.52(0.41, 0.65)***	
Hypertension							ar te		
No	184	32174	5.72	108	37634	2.87	(0.41, 0.66)***	0.57(0.45, 0.72)***	
Yes	421	16661	25.3	233	19639	11.9	g0.53(0.45, 0.62)***	0.57(0.49, 0.67)***	
Hyperlipidemia							025 a		
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	0.5 3 (0.41, 0.63)***	0.51(0.41, 0.63)***	
Congestive heart							e Bii		
failure							bliog		
No	513	46595	11.0	285	54590	5.22	0.53 (0.44, 0.59)***	0.55(0.47, 0.64)***	
Yes	92	2241	41.1	56	2683	20.9	0.6 ² /2 ^{(0.44, 0.85)***}	0.65(0.47, 0.92)***	
Depression		For peer review	/ only - http	o://bmjopen.b	omj.com/site/about/g	guidelines.xh	tml G		
No	523	44638	11.7	303	52396	5.78	0.54(0.47, 0.62)***	0.59(0.51, 0.67)***	

							njo	
Yes	82	4198	19.5	BMJ Open 38	4877	7.79	a 0.4 3 (0.30, 0.64)***	Page 38 of 44 0.48(0.32, 0.72)***
Anxiety							2023 pyrig	
No	442	38718	11.4	248	46073	5.38	<u>-0</u> .5 4 (0.44, 0.60)***	0.56(0.48, 0.66)***
Yes	163	10117	16.1	93	11200	8.30	P.5 (0.43, 0.71)***	0.57(0.44, 0.74)***
Alcoholism							on 1 ding	
No	596	48177	12.4	330	56529	5.84	q).5 ; (0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	9	659	13.7	11	744	14.8	נג דיין 1.12(0.47, 2.67)	1.25(0.50, 3.09)
Tobacco use							ary 2 seigr	
No	603	48655	12.4	341	57090	5.97	a b b c (0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	2	181	11.1	0	182	0.00	Dov to te	
Obesity							vnlo; xt a	
No	598	48412	12.4	338	56737	5.96	0252 (0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	7	424	16.5	3	536	5.60	DE (0.10, 1.49)	0.40(0.14, 1.19)
Atrial fibrillation							m ht BES)	
No	576	46291	12.4	320	54553	5.87	5 .5 <u>5</u> (0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	29	2545	11.4	21	2720	7.72	a.72(0.41, 1.26)	0.70(0.38, 1.30)
Drugs used							ining	
Oral steroid							g, an	
No	318	17828	17.8	166	21844	7.60	a D.4 a (0.40, 0.58)***	0.53(0.44, 0.64)***
Yes	287	31008	9.26	175	35429	4.94	€ (0.46, 0.68)***	0.59(0.49, 0.72)***
NSAID							Jun	
No	216	7329	29.5	105	9509	11.0	a.44(0.37, 0.58)***	0.54(0.43, 0.69)***
Yes	389	41506	9.37	236	47764	4.94	ૡૢ).5 § (0.47, 0.64)***	0.56(0.48, 0.66)***
Statin							25 at	
No	586	45820	12.8	322	54040	5.96	0.5	0.56(0.49, 0.64)***
Yes	19	3016	6.30	19	3233	5.88	0.9 a (0.50, 1.79)	0.97(0.49, 1.95)
Conventional							Bib	
DMARDS							liogr	
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	0.5 5 (0.46, 0.68)***	0.58(0.47, 0.71)***
Biological DMARDs		For peer revie	ew only - http:	://bmjopen.bmj.c	:om/site/abou	t/guidelines.xhti	ml de	

D					DMI O			njop d by	
Page 39 of 44	No	591	44821	13.2	336	ⁿ 52599	6.39	3 0.5 3 (0.46, 0.60)***	0.58(0.50, 0.66)***
	Yes	14	4014	3.49	5	4674	1.07	J.28(0.10, 0.79)*	0.26(0.09, 0.80)**
2	Abbreviation: IR, in	cidence rate per 1	,000 person	-years; SHR	, subhazard r	atio; CI, confid	lence interva	-075	
3	Adjusted SHR: adju	sted for accepted	acupuncture	e, age, sex, c	omorbidities,	, and drugs use	d in the com	pearling risks regression m	odels.
4 5								on 1 ding	
6	*: p < 0.05; **: p <	0.01; *** p < 0.00)]					3 Fe	
7 8	Abbreviation: Nons	teroidal anti-inflai	mmatory dru	igs (NSAID	s), DMARD	(disease-modif	ying antirhei	ingaticedrugs).	
9								ary 2 seigr s rela	
10								024. ated	
12								Dov to te	
13 14								vnlo stra	
15								adec rieu	
16 17								ata r	
18								m ht BES)	
19 20								tp://	
21								omjo	
22								ining	
24								g, an	
26								d sii	
27 28								√ on	
29								Jun	
30 21								e 11 hnol	
32								, 202 ogie	
33 24								s. 5 at	
35								Age	
36 27								nce	
38								Bibl	
39								iogr	
40 41								aphi	
42								que	
43 44			For peer revi	ew only - http	://bmjopen.bm	j.com/site/about/	/guidelines.xht	ml de	
45 46									
40									

 $^{1}_{2}$ Supplementary Table 3. Characteristics of rheumatoid arthritis patients according to accept acupuncture in 3un-matching.

4		Rheumatoi	d Arthritis			
5		Accepted ac	cupuncture			
7 Variable	No (n =	=22218)	Yes (n =	=12266)		
	n	%	n	%	_	
Gender						
¹² Women	16702	75.2	10109	82.4	0.18	
4 Men	5516	24.8	2157	17.6	0.18	
Age group					rote	
18-39	2994	13.5	1767	14.4	0.03 e	
40-59	12351	55.6	7762	63.3	0.16	
$20 \ge 60$	6873	30.9	2737	22.3	0.20 by	
²¹ Mean±SD (years)	56.7	±14.7	54.3±	13.3	0.17 ^{ri} g	
22 2Baseline Comorbidity					t, inc	
²⁴ Diabetes mellitus	4117	18.5	2260	18.4	0.003	
26 Hypertension	8857	39.9	4632	37.8	0.04 ng	
²⁷ Hyperlipidemia	5610	25.3	3593	29.3	0.09 g	
29 Congestive heart failure	1698	7.64	736	6.00	0.07	
³⁰ Depression	1901	8.56	1394	11.4	0.09	
Anxiety	4591	20.7	3118	25.4	0.11 d	
³³ Alcoholism	422	1.90	244	1.99	0.01	
35 Tobacco used	146	0.66	84	0.68	0.003 a	
³⁶ Obesity	188	0.85	163	1.33	0.05 da	
³⁷ Atrial fibrillation	1102	4.96	845	6.89	0.08 <u>a</u>	
³⁹ Drug used					ning	
41 Oral steroid	10814	48.7	6946	56.6	0.16 Ž	
⁴² NSAID	13907	62.6	9532	77.7	0.34 ^{tra} in	
¹³ Statin	828	3.73	688	5.61	ing, 0.09	
⁴⁵ Conventional DMARDS					and	
47 Hydroxychloroquine	9299	41.9	6059	49.4	0.15 Sin	
⁴⁸ Sulfasalazine	7210	32.5	4606	37.6	0.11 ar	
50 Methotrexate	14	0.06	11	0.09	0.01 ech	
51 52 Leflunomide	1309	5.89	973	7.93	0.08 0.00	
53 D-penicillamine	196	0.88	138	1.13	0.02 g	
54 55 Azathioprine	385	1.73	229	1.87	0.01	
66 Mycophenolate	10	0.05	7	0.06	0.01	
⁵⁷ ₅₈ Cyclosporine	816	3.67	594	4.84	0.06	
59Biological DMARDs						

Pag	ge 41 of 44	BMJ Op	ben			
	Etanercept	941	4.24	706	5.76	0.07
1 2	Adalimumab	345	1.55	202	1.65	0.01
<u>з</u> Т	ypes of acupuncture					
4 5	Manual acupuncture			10604	86.45	
6	Electroacupuncture			407	3.32	
7 8 9e]	Combination of manual acupuncture and lectroacupuncture			1255	10.23	
10 11 1 2	Ouration between rheumatoid arthritis date nd index, days (mean, median)	(981.29	9, 668.0)	(1047.36	5, 688.5)	
13 14	cupuncture visits, (mean, meidan)			(10.43,	, 3.00)	

 Table Index, Gays (mean, median)
 (10.43, 3.00)

 Accupuncture visits, (mean, median)
 (10.43, 3.00)

 The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared of polymetric introductions. Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

 State
 State

 State
 Stat

¹Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted 3 acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in $\frac{4}{5}$ un-matching.

6 Veriable	No. of event		Crude [*]			$\mathbf{Adjusted}^{\dagger}$	
7 Variable 8	(n=1441)	SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
⁹ Accepted acupunctu	re						
10 11 No	1080	1.00	reference		1.00	reference	
12 Yes	361	0.48	(0.42, 0.53)	< 0.001	0.65	(0.58, 0.74)	< 0.001

¹Crude SHR^{*} represented relative subhazard ratio;

¹Adjusted SHR[†] represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, ¹Comorbidities, and drugs used in competing-risks regression models.

19	
20	
20	
21	
22	
23	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
33	
34	
35	
36	
27	
37	
38	
39	
40	
41	
42	
43	
13	
44	
45	
46	
47	
48	
49	
50	
51	
52	
55	
J4 FF	
55	
56	
57	
58	
59	
60	



3 4

		BMJ Open BMJ Open BMJ Open BMJ Open BMJ Open BMJ Open	Page 44 c
	ST	ROBE 2007 (v4) Statement—Checklist of items that should be included in reports of case acontrol studies	
Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(b) Provide in the abstract an informative and balanced summary of what was done and what 🛪 🖧 und	1-5
Introduction		2022 Inen Iateo	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods		an eriede	
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and contropselection. Give the rationale for the choice of cases and controls	9-10
		(b) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier diagnostic criteria, if	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how matching of cases and controls was addressed	11
		(e) Describe any sensitivity analyses	11
Results		Ŭ a a a a a a	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

 njopen-2023. d by copyrigl

ographique de l

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, exagined for eligibility, confirmed	12-13
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precessing (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningfu	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion		ning S) - tr	
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of a alyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information		lar on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in centrols and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published exan bless of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.grg/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.sections.

BMJ Open

Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-075218.R2
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2023
Complete List of Authors:	Huang, Chia-Yu; China Medical University, Huang, Ming-Cheng; China Medical University Hospital, Department of Chinese Medicine Liao, Hou-Hsun; China Medical University Lin, Cheng-Li; China Medical University Hospital; China Medical University Lee, Yu-Chen; China Medical University, Graduate Institute of Acupuncture Science; China Medical University Hospital, Acupuncture Department Zimmerman, Gregory; China Medical University Wu, Mei-Yao; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University
Primary Subject Heading :	Complementary medicine
Secondary Subject Heading:	Rheumatology, Neurology
Keywords:	Stroke < NEUROLOGY, COMPLEMENTARY MEDICINE, RHEUMATOLOGY

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1	Acupuncture decreased the risk of ischemic stroke in patients with
2	rheumatoid arthritis: a nationwide propensity score-matched study
3	
4	Authors:
5	Chia-Yu Huang, M.D., Ph.D. ^{1,2†} , Ming-Cheng Huang, M.D., Ph.D. ^{1,3†} , Hou-Hsun
6	Liao, M.D., M.S. ^{2,3} , Cheng-Li Lin, M.S. ^{4,5} , Yu-Chen Lee, M.D., Ph.D. ^{3,6} , Gregory
7	Zimmerman, M.S. ⁶ , Mei-Yao Wu, M.D., Ph.D. ^{3,7,8,††} , Hung-Rong Yen, M.D.,
8	Ph.D. ^{1,3,8,9,10,††}
9	[†] Chia-Yu Huang and Ming-Cheng Huang contributed equally to this work and share
10	first authorship.
11	[†] [†] Mei-Yao Wu and Hung-Rong Yen contributed equally to this work and share
12	corresponding authorship.
13	
14	Affiliations:
15	¹ Department of Family Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi
16	Medical Foundation, Taichung, Taiwan
17	² Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of
18	Chinese Medicine, China Medical University, Taichung, Taiwan
19	³ Department of Chinese Medicine, China Medical University Hospital, Taichung,
20	Taiwan
21	⁴ Management Office for Health Data, China Medical University Hospital, Taichung,
22	Taiwan.
23	⁵ College of Medicine, China Medical University, Taichung, Taiwan
24	⁶ Graduate Institute of Acupuncture Science, College of Chinese Medicine, China

BMJ Open

25 Medical University

1 2		
3 4	1	⁷ School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine,
5 6 7	2	China Medical University, Taichung, Taiwan
7 8 9	3	⁸ Research Center for Traditional Chinese Medicine, Department of Medical Research,
10 11	4	China Medical University Hospital, Taichung, Taiwan
12 13	5	⁹ Chinese Medicine Research Center, China Medical University, Taichung, Taiwan
14 15 16	6	
17 18	7	Corresponding authors:
19 20	8	Hung-Rong Yen, M.D., Ph.D.
21 22	9	School of Chinese Medicine, College of Chinese Medicine, China Medical University,
23 24 25	10	Taichung, Taiwan
26 27	11	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
28 29	12	Tel.: +886-4-22053366 ext. 3313
30 31 22	13	Fax: +886-4-22365141
32 33 34	14	E-mail: hungrongyen@gmail.com
35 36	15	or
37 38	16	Mei-Yao Wu, M.D., Ph.D.
39 40 41	17	School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, China
42 43	18	Medical University, Taichung, Taiwan
44 45	19	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
46 47 48	20	Tel.: +886-4-22052121 ext. 4561
40 49 50	21	Fax: +886-4-22365141
51 52	22	E-mail: meiyaowu0919@gmail.com
53 54	23	
55 56 57	24	E-mail addresses for all authors:
58 59	25	Chia-Yu Huang: dochuangcharlie@gmail.com
60	26	Ming-Cheng Huang: mchuang1128@gmail.com 2

2	
3 4 5	1
5 6 7	2
, 8 9	3
10 11	4
12 13	5
14 15	6
16 17	7
18 19 20	8
20 21 22	9
23 24	10
25 26	10
27 28	11
29 30	12
31 32	13
33 34	14
35 36	15
37 38	16
39 40	17
41 42	18
43 44 45	19
45 46 47	20
48 49	21
50 51	22
52 53	22
54 55	23
56 57	24
58 59	25
60	26

Keywords: Acupuncture; Cardiovascular diseases; National Health Insurance

Word count: Abstract: 275; Text: 2490; No of Tables: 1; No of Figures: 2

Research Database; Rheumatoid arthritis; Stroke.

Hou-Hsun Liao: a202098@cmu.edu.tw

Cheng-Li Lin: orangechengli@gmail.com

Yu-Chen Lee: d5167@mail.cmuh.org.tw

Gregory Zimmerman: gregzlac@gmail.com

Mei-Yao Wu: meiyaowu0919@gmail.com

Hung-Rong Yen: hungrongyen@mail.cmu.edu.tw

Running title: Acupuncture Reduced the Risk of Stroke

2		
3 4	1	Abstract
5	_	
6 7	2	Objectives: The purpose of this study was to demonstrate that acupuncture is
8 9	3	beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid
10 11	4	arthritis (RA).
12 13	5	Design: This is a propensity score-matched cohort study.
14 15 16	6	Setting: This is a nationwide population-based study.
17 18	7	Participants: The patients with RA diagnosed between 1 January 1997 and 31
19 20	8	December 2010 through the National Health Insurance Research Database.
21 22	9	Interventions: The patients who were administered acupuncture therapy from the
23 24 25	10	initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were
25 26 27	11	included in the acupuncture cohort. Patients who did not receive acupuncture
28 29	12	treatment during the same time interval were regarded as the no-acupuncture cohort.
30 31	13	Primary outcome measures: A Cox regression model was used to adjust for age, sex,
32 33 34	14	comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of
35 36	15	IS between these two cohorts through competing-risks regression models.
37 38	16	Results: After a 1:1 propensity score match, a total of 23,226 patients were identified.
39 40	17	The basic characteristics of these patients were similar. A lower cumulative incidence
41 42 43	18	of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$;
44 45	19	immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the end, 341
46 47	20	patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in
48 49	21	the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic
50 51 52	22	stroke (adjusted SHR, 0.57; 95% CI, 0.50-0.65). The advantage of lowering ischemic
53 54	23	stroke incidence through acupuncture therapy in RA patients was independent of sex,
55 56	24	age, types of drugs used, and comorbidities.
57 58	25	Conclusions: This study showed the beneficial effect of acupuncture in reducing the
59 60	26	incidence rate of ischemic stroke in patients with RA.

2	
3	
4	
6	
7	
8	
9	
10	
12	
13	
14	
15	
16 17	
18	
19	
20	
21	
23	
24	
25	
26 27	
28	
29	
30	
31 32	
33	
34	
35	
30 37	
38	
39	
40	
41 42	
43	
44	
45	
46 47	
48	
49	
50	
51 52	
53	
54	
55	
50 57	
58	
59	
60	

2

4

5

1 Strengths and limitations of this study:

• Our research disclose the possible long-term effect from acupuncture in stroke

3 prevention which could not be investigated from clinical trial.

• Lower ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.

• The causality could not be proved directly as clinical trial through our study design.

7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	-
	5

1 Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness [1]. The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD) [2-5]. Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke [6-11]. Comparing to general population, stroke is more common noted in the RA patients [12]. The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively [13-15]. But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue to clinical doctors and patients [18]. The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF- α inhibitor) and anakinra (IL-1 inhibitor) [3,5,19]. And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients [18]. But some of them could bring the complications in the bone marrow to cause thrombocytopenia [20]. The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, 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 founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture [26]. Furthermore, secondary stroke prevention is also noted from acupuncture therapy in the Taiwanese [27]. And the hypothesis in the acupuncture to lower stroke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population [28]. In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database [29]. We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

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. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or 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 a 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 (CMUH104-REC2-115).

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

21 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 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA 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 minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient 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 no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

17 Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and \geq 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401-405), hyperlipidemia (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,

BMJ Open

2	
3	
1	
- -	
2	
6	
7	
8	
9	
10	
10	
11	
12	
13	
14	
15	
16	
17	
17	
18	
19	
20	
21	
22	
25	
23	
24	
25	
26	
27	
28	
20	
29	
30	
31	
32	
33	
34	
25	
22	
30	
37	
38	
39	
40	
Δ1	
40	
42	
43	
44	
45	
46	
47	
., ۸۵	
40	
49	
50	
51	
52	
53	
51	
54 57	
55	
56	
57	
58	
59	
60	

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 ischemic
 stroke (ICD-9-CM: 433-438) were compared between acupuncture and
 non-acupuncture cohort of RA patients.

5

6 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

11

12 Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline 13 14 characteristics of the acupuncture and no-acupuncture cohorts as previously described 15 [30]. A negligible difference in mean values or proportions between the two cohorts 16 was defined as less than 0.1 standard deviation (SD). A competing-risks regression 17 models was performed to estimate the crude and adjusted subhazard ratios (SHRs) of 18 acupuncture therapy, age, sex, comorbidities, and types of drugs used. The 19 Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 20 21 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical 22 Computing, Vienna, Austria) to perform statistical analyses and create the figures. 23 Statistical significance was defined as p < 0.05 in two-tailed tests.

- 25 Patient and Public Involvement
 - 26 None

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (Fig. 1). The baseline characteristics of both cohorts are presented in Table 1, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% 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, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (Supplementary Table 1). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

BMJ Open

cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, p < 0.001, **Fig. 2**).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50-0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥ 40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44-0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in **Supplementary Table 3** and **4**. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the 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 ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA [32]. Inflammation is a consistent and independent predictor of CVD in RA [33]. TNF- α is a cytokine that mediates inflammation 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 CVD risk in RA [37]. Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

There are a couple evidences and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the amounts 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 the RA patients, acupuncture was found to reduce TNF-a and vascular endothelial growth factor to improve the inflammation of RA [43]. In

animal studies, acupuncture reduced inflammation in collagen-induced arthritis model [44-46]. Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin [47], adenosine [48] and orexin [49], but also reduce inflammation through dopamine [50]. On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [51,52]. If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke [53].

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, 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 minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. And the algorithm for risk to develop cardiovascular events, such as the Framingham Risk Score is hard to form, because of lacking the above information. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies
BMJ Open

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (Supplementary Fig. 1) [55,56]. Further clinical trials with standardized acupoints should be conducted based on the findings of this study. And the difference of treatment results among various types of interventions could not be found from our database which did not belong to our result measure. The evidence of treatment dose of acupuncture therapy is still establishing, scurs the to_F thus we did not discuss the topic in here.

Our study demonstrates that the ischemic stroke risk could be reduced by

acupuncture treatment in patients with RA in Taiwan. The possible mechanism may

attenuates cardiovascular disease, including ischemic stroke. It also offers important

reduce pro-inflammatory cytokines through acupuncture therapy which could

ideas for more comprehensive studies in the future.

Conclusions

BMJ Open

Ethics Approval Statement

2 The Research Ethics Committee of China Medical University and Hospital in Taiwan
3 approved this study (CMUH104-REC2-115).

Competing Interests: 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.

9 Funding

This work was financially supported by the "Chinese Medicine Research Center, China Medical University" from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-1). This study was also supported in part by China Medical University (CMU103-BC-4-2, CMU105-BC-1-1, CMU105-BC-1-2), China Medical University Hospital (DMR-107-011, DMR-110-002, and DMR-111-105), and Ministry of Science and Technology (MOST108-2638-B-039-001-MY2, MOST107-2320-B-039-037, MOST108-2320-B-039-021, and MOST110-2321-B-

039-003). This study is also supported in part by Taiwan Ministry of Health and
Welfare Clinical Trial Center (MOHW111-TDU-B-212-134004), Taiwan. None of
the funders and institutions listed had a role in the design and conduct of the study;
collection, management, analysis, and interpretation of the data; preparation, review,
or approval of the manuscript; and decision to submit the manuscript for publication.

24 Acknowledgement

25 This study was based in part on data from the National Health Insurance Research
 26 Database, provided by the National Health Insurance Administration, Ministry of 17

BMJ Open

2
2
4
5
6
7
8
9
10
10
11
12
13
14
15
16
17
10
10
19
20
21
22
23
24
25
25
20
27
28
29
30
31
32
22
22
34
35
36
37
38
39
10
40
41
42
43
44
45
46
47
77 10
40
49
50
51
52
53
54
55
55
20
57
58

59 60 Health and Welfare, and managed by National Health Research Institutes. The
 interpretation and conclusions contained herein do not represent those of National
 Health Insurance Administration, Ministry of Health and Welfare, or National Health
 Research Institutes.

5

6 Authors' contributions

7 CYH and MCH contributed equally. MCH contributed to conception of the study, 8 participated in the interpretation of clinical data and drafted the manuscript. CYH 9 contributed to conception of the study, participated in the interpretation of clinical 10 data and drafted the manuscript. HHL participated in the interpretation of clinical data 11 and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the 12 manuscript. MYW contributed to design of the study, participated in the interpretation 13 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 14 15 project, contributed to conception and design of the study and finalized the 16 manuscript. MYW and HRY contributed equally as co-corresponding authors.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

17

18 Data availability

19 The datasets generated during and/or analysed during the current study are available

20 from the corresponding author on reasonable request.

References

- Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990; 16:513-37.
- Sesin CA, Bingham CO, 3rd. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2005;35:185-196.
- 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 Jun* 2008;15:762-784.
 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;69:1010-1014.
- 5. Smolen JS, Landewe 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;69:964-975.
- 6. Avina-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;59:1690-1697.
- 7. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular

BMJ Open

events in patients with rheumatoid arthritis: a meta-analysis of observational studies.
Ann Rheum Dis 2012;71:1524-1529.
8. de Groot L, Posthumus MD, Kallenberg CG, et al. Risk factors and early detection
of atherosclerosis in rheumatoid arthritis. Eur J Clin Invest 2010;40:835-842.
9. Meune C, Touze E, Trinquart 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;103:253-261.
10. Peters MJ, Symmons DP, 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;69:325-331.
11. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best
Pract Res Clin Rheumatol 2011;25:469-483.
12. 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;59:1090-1096.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

13. 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;41:863-877.

- 14. 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;33:248-255
- 15. Lai CH, Lai MS, Lai KL, et al. Nationwide population-based epidemiologic study of rheumatoid arthritis in Taiwan. *Clin Exp Rheumatol* 2012;30:358-363.
- 16. Liou TH, Huang SW, Lin JW, 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* 20113;72:541-546.
- Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. *Curr Treat Options Neurol* 2015;17:356.
- 19. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591-2602.
- 20. Bowman SJ. Hematological manifestations of rheumatoid arthritis. *Scand J Rheumatol* 2002;31:251-259.
- 21. Seca S, Patricio M, Kirch S, et al. Effectiveness of Acupuncture on Pain,

3
4
5
6
7
, Q
0
9
10
11
12
13
14
15
16
17
18
19
20
21
27
∠∠ ??
23
24
25
26
27
28
29
30
31
32
33
34
35
36
50 27
3/
38
39
40
41
42
43
44
45
46
47
48
49
50
51
57
52 52
55 54
54
55
56
57
58
59
60

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.

- 22. Tam LS, Leung PC, Li TK, et al. Acupuncture in the treatment of rheumatoid arthritis: a double-blind controlled pilot study. *BMC Complement Altern Med* 2007;7:35.
- 23. 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;15:187-193.
- 24. Chou PC, Chu HY. Clinical Efficacy of Acupuncture on Rheumatoid Arthritis and Associated Mechanisms: A Systemic Review. *Evid Based Complement Alternat Med* 2018;8596918.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

25. Huang CY, Wu MY, Huang MC, 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;14:1-9.
26. Huang MC, Pai FT, Lin CC, 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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

3
4
5
6
0
/
8
9
10
11
12
13
14
15
16
10
17
18
19
20
21
22
23
23
24
25
26
27
28
29
30
31
32
33
31
24 27
35
36
37
38
39
40
41
42
<u>4</u> 2
43
44
45
46
47
48
49
50
51
52
52
52
54
55
56
57
58
59
60

1 2

> 27. Shih CC, Liao CC, Sun MF, et al. A Retrospective Cohort Study Comparing Stroke Recurrence Rate in Ischemic Stroke Patients With and Without Acupuncture Treatment. *Medicine (Baltimore)* 2015;94:e1572.

> 28. Huang CY, Wu MY, Chang CL, 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;63:1-9.

29. Huang CY, Wu MY, Kuo YH, 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.

30. Wu MY, Huang MC, Liao HH, 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.

31.Wu MY, Lee YC, Lin CL, 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.

32. 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*

2	
3	
4	2017;76:17-28.
5	
6	
7	33 Karpouzas GA Ormseth SR Hernandez E et al Impact of Cumulative
8	
9	
10	Inflammation Cardiac Risk Factors and Medication Exposure on Coronary
11	initialinitation, Cardiae Nisk I actors, and Wedleation Exposure on Coronary
12	
13	Athorogalarogic Prograssian in Phaymatoid Arthritic Arthritic Phaymatol
14	Autoroscierosis Progression in Kileumatolu Artinitus. Artinitus Kileumator
15	
16	2020.72.400 409
17	2020;72:400-408.
18	
10	
20	34. Visvanathan S, Rahman MU, Keystone E, et al. Association of serum markers
20	
21	
22	with improvement in clinical response measures after treatment with golimumab in
23	
24	
25	patients with active rheumatoid arthritis despite receiving methotrexate: results
26	
27	
28	from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.
29	
30	
31	35 Kleinert S Tony HP Krause A et al Impact of national disease characteristics
32	set filometes, fong fil, filouse fi, et un impact of panent and abouse enalacteristics
33	
34	on the range tic success during adaligning treatment of natients with rheumatoid
35	on therapeutie success during adaminantab treatment of patients with meanatola
36	
37	arthritic: data from a German noninterventional observational study. <i>Phaumatal Int</i>
38	artifittis. data from a Ociman nominer ventional observational study. <i>Kneumuloi mi</i>
39	
40	2012.22.2750.2767
41	2012,52.2759-2767.
42	
42	
45	36. Wijbrandts CA, Dijkgraaf MG, Kraan MC, et al. The clinical response to
44	
45	
40	infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour
47	
48	
49	necrosis factor alpha expression in the synovium. Ann Rheum Dis
50	
51	
52	2008;67:1139-1144.
53	
54	
55	37. Karpouzas GA, Ormseth SR, Hernandez E, et al. Biologics may prevent
56	1 ····································
57	
58	cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque
59	carate rassular events in meanatora arannas by minorang coronary plaque
60	
	24

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

formation and stabilizing high-risk lesions. *Arthritis Rheumatol* 2020;72, 1467-1475.

- 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;177:508-515.
 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;179:1388-1397.

- 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;27:103-105.
- 42. Lee H, Lee JY, Kim YJ, et al. Acupuncture for symptom management of rheumatoid arthritis: a pilot study. *Clin Rheumatol* 2008;27:641-645.
- 43. Ouyang BS, Gao J, Che JL, 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;17:505-509.
 44. He X, Huang L, Qiu S, et al. beta-Endorphin attenuates collagen-induced arthritis

BMJ Open

partially by inhibiting peripheral pro-inflammatory mediators. Exp Ther Med
2018;15:4014-4018.
45. Ye TS, Du ZH, Li ZH, et al. Repeated Electroacupuncture Persistently Elevates
Adenosine and Ameliorates Collagen-Induced Arthritis in Rats. Evid Based
Complement Alternat Med 2016;3632168.
46. Li J, Li J, Chen R, et al. Targeting NF-kappaBeta 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;13:883-888.
49. Chen YH, Lee HJ, Lee MT, et al. Median nerve stimulation induces analgesia via
orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. Proc
<i>Natl Acad Sci U S A</i> 2018;115:E10720-E9.
50. Torres-Rosas R, Yehia G, Pena G, et al. Dopamine mediates vagal modulation of
the immune system by electroacupuncture. Nat Med 2014;20:291-295.
51. Hsieh CH. The effects of auricular acupressure on weight loss and serum lipid
levels in overweight adolescents. Am J Chin Med 2010;38:675-682.
26

52. Flachskampf FA, Gallasch J, Gefeller O, et al. Randomized trial of acupuncture	to .
lower blood pressure. Circulation 2007;115:3121-3129.	
53. Semb AG, Ikdahl E, Wibetoe G, et al. Atherosclerotic cardiovascular disease	
prevention in rheumatoid arthritis. Nat Rev Rheumatol 2020;16:361-379.	P
54. Rassen JA, Shelat A.A, Myers J, et al. One-to-many propensity score matching i	n cted
cohort studies. <i>Pharmacoepidemiol Drug Saf</i> 2012;21:69-80.	by соруг
55. Tou SI, Huang CY, Yen HR. Effect of Acupoint Stimulation on Controlling Pair	ight, inc
from Heel Lance in Neonates: A Systematic Review and Meta-Analysis of	luding fc
Randomized Controlled Trials. Children 2023;10:1024.	Ensei uses r
56. Lin JG, Li TM, Hsu SF. Newly Edited Color Book of Acupuncture and	gnement blated to
Moxibustion; JYIN Publishing Company: Taipei, Taiwan, 2009.	: Superie text and
	ur (ABE: data mi
	s) ning, Al
	training
	, and sim
	nilar tech
	nologies
	ç,
27	-
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

	G4 1 1					
X7 · 11	Ac	Acupuncture treatment				
variable	No (n =	= 11613)	Yes (n =	11613)	difference	
	n	%	n	%	unierence	
Sex						
Women	9499	81.8	9478	81.6	0.01	
Men	2114	18.2	2135	18.4	0.01	
Age group						
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 \pm 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	
Hyperlipidemia	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	

4:. whather T-1-1 1 01 £ ..1 : 1 +ŀ y

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Cyclosporine	555	4 78	544	4 68	0 004
Biological DMARDs	200	1.70	211	1.00	0.001
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid					
arthritis diagnosis and index,	(1078.52	2, 795.0)	(1065.18	, 707.0)	0.32
days (mean, median)					
Acupuncture visits (mean,		-	(9.83,	3.00)	
median)					

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD

(disease-modifying antirheumatic drugs).

Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis 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.

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

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Figures



F



BMJ Open

BMJ Open 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.

	No. of	Crude [*]				Adjusted [†]		
Variable	event (n = 946)	SHR	(95% CI)	p-value	218 on 1 Slang	(95% CI)	p-value	
Acupuncture treatment					3 Fei for u			
No	605	1.00	reference		1 Sobs Tra	reference		
Yes	341	0.52	(0.46, 0.60)	< 0.001		(0.49, 0.65)	< 0.001	
Sex					024. ted t			
Women	714	1.00	reference			reference		
Men	231	1.44	(1.24, 1.67)	< 0.001		(1.14, 1.54)	< 0.001	
Age group					ided id da			
18-39	13	1.00	reference		1 \$ 0 \$ 5	reference		
40-59	372	7.17	(4.14, 12.4)	< 0.001		(3.44, 10.4)	< 0.001	
≥ 60	561	28.1	(16.3, 48.6)	< 0.001	1 9 .7	(8.38, 25.7)	< 0.001	
Baseline Comorbidity					ul tra			
(ref = no comorbidity)					ining			
Diabetes mellitus	334	2.64	(2.31, 3.01)	< 0.001	ျမ္မာ8	(1.36, 1.82)	< 0.001	
Hypertension	654	3.96	(3.45, 4.54)	< 0.001	2 2 2 0 S	(1.79, 2.47)	< 0.001	
Hyperlipidemia	371	1.94	(1.70, 2.21)	< 0.001		(0.93, 1.25)	0.30	
Congestive heart failure	148	3.18	(2.67, 3.79)	< 0.001	ן 1 פ ון 1	(1.08, 1.59)	0.006	
Depression	120	1.46	(1.21, 1.77)	< 0.001	1012 1	(0.91, 1.37)	0.28	
Anxiety	256	1.40	(1.21, 1.61)	< 0.001	0°°°99'28	(0.85, 1.16)	0.94	
Alcoholism	20	1.48	(0.95, 2.29)	0.08	ອ 1.46 ຊ	(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 e	(0.58, 2.08)	0.77	
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89 <mark>B</mark>	(0.66, 1.19)	0.43	
Drugs used					iogr			
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51 <mark>ap</mark>	(0.42-0.62)	< 0.0001	
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24 g	(0.11-0.51)	0.0002	
Statin	329 For p	eer review 1.04	only - http://bmjopen.bmj.com (0.92-1.17)	/site/about/guideline 0.5575	es.xhtml 0.65 e	(0.58-0.74)	< 0.0001	

Page 35 of 43	Conventional DMARDS			BMJ Open		ıjopen I by co			
	Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001	PV 77022	(0.60, 0.81)	< 0.001	
1 2	Sulfasalazine	235	0.47	(0.41, 0.54)	< 0.001	0.80 5.07	(0.68, 0.94)	0.007	
3	Methotrexate	2	1.88	(0.50, 7.04)	0.35	יים 2 18 31 <u>1</u> 5	(0.84, 11.9)	0.08	
4 5	Leflunomide	18	0.22	(0.14, 0.35)	< 0.001		(0.22, 0.54)	< 0.001	
6	D-penicillamine	11	0.85	(0.46, 1.53)	0.53		(0.61, 1.88)	0.05	
7 8	Azathioprine	9	0.39	(0.20, 0.75)	0.004		(0.40, 1.49)	0.44	
9	Mycophenolate	0	-	-		ary 2 seigi s rela	-		
10 11	Cyclosporine	35	0.62	(0.44, 0.87)	0.005		(0.99, 1.98)	0.06	
12	Biological DMARDs					ent of to to			
13 14	Etanercept	16	0.27	(0.16, 0.44)	< 0.001		(0.31, 0.83)	0.007	
15	Adalimumab	3	0.18	(0.06, 0.57)	0.003	not a dec	(0.14, 1.34)	0.15	
16 17	Conventional DMARDS					d fro r (AE ata I			
18	Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001		(0.60, 0.81)	< 0.001	
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	Adjusted SHR [†] represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age set comorbidities, and drugs used in competing-risks regression models. Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumation of the set of the s								

BMJ Open Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke Brite umatoid 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			Rheum	Compared with no	Compared with non-acupuncture users				
	No (n = 11613)				Yes		Crude SHR	Adjusted SHR	
					(n = 11613)		on 1: ding		
	Event	Person years	\mathbf{IR}^{\dagger}	Event	Person years	\mathbf{IR}^{\dagger}	of Fe (95% CI)	(95% CI)	
							uary es re		
Total	605	48836	12.4	341	57273	5.95	a b c (0.46, 0.60)***	0.57(0.50, 0.65)***	
Sex							1. Dc		
Women	460	40274	11.4	254	46907	5.41	D <u> </u>	0.58(0.49, 0.67)***	
Men	145	8562	16.9	87	10366	8.39	a) (0.42, 0.71)***	0.54(0.41, 0.70)***	
Age group							ed fr ur (A data		
18-39	5	8734	0.57	8	8576	0.93		1.45(0.44, 4.76)	
40-59	226	29529	7.65	146	37225	3.92	4 0.5 5 (0.43, 0.66)***	0.54(0.44, 0.66)***	
≥ 60	374	10573	35.4	187	11472	16.3	₹0.5 ⁵ (0.46, 0.65)***	0.58(0.48, 0.69)***	
Baseline Comorbidity							jope		
Diabetes mellitus							ng,		
No	383	41083	9.32	229	48060	4.76	a).55(0.47, 0.65)***	0.60(0.51, 0.71)***	
Yes	222	7753	28.6	112	9213	12.2	S 0.4 7 (0.38, 0.59)***	0.52(0.41, 0.65)***	
Hypertension							on Ju		
No	184	32174	5.72	108	37634	2.87	g0.5a(0.41, 0.66)***	0.57(0.45, 0.72)***	
Yes	421	16661	25.3	233	19639	11.9 -	g).53 (0.45, 0.62)***	0.57(0.49, 0.67)***	
Hyperlipidemia							025 jies.		
No	366	36970	9.90	209	43496	4.81	0.5	0.61(0.51, 0.72)***	
Yes	239	11866	20.1	132	13777	9.58	0.5 ³ (0.41, 0.63)***	0.51(0.41, 0.63)***	
Congestive heart							ё <u>В</u>		
failure							blio		
No	513	46595	11.0	285	54590	5.22	0.5 ⁵ (0.44, 0.59)***	0.55(0.47, 0.64)***	
Yes	92	2241	41.1	56	2683	20.9	0.6 ² (0.44, 0.85)***	0.65(0.47, 0.92)***	
Depression		For peer review	only - http)://bmjopen.b	mj.com/site/about/c	uidelines.xh [.]	tml ନ		
No	523	44638	11.7	303	52396	5.78	$0.5\overline{4}(0.47, 0.62)^{***}$	0.59(0.51, 0.67)***	

								njo	
Page 37 of 43	Yes	82	4198	19.5	BMJ Open 38	4877	7.79	a 0.4 3 (0.30, 0.64)***	0.48(0.32, 0.72)***
1	Anxiety							2023 Syrig	
2	No	442	38718	11.4	248	46073	5.38	<u>-</u> 0.5 % (0.44, 0.60)***	0.56(0.48, 0.66)***
3	Yes	163	10117	16.1	93	11200	8.30	2 0.5 2 (0.43, 0.71)***	0.57(0.44, 0.74)***
4 5	Alcoholism							on 1 ding	
6	No	596	48177	12.4	330	56529	5.84	q).5 ; (0.45, 0.59)***	0.56(0.49, 0.64)***
8	Yes	9	659	13.7	11	744	14.8	us my 1.12(0.47, 2.67)	1.25(0.50, 3.09)
9	Tobacco use							seigr seigr	
10 11	No	603	48655	12.4	341	57090	5.97	a) 5 2 (0.46, 0.60)***	0.57(0.50, 0.65)***
12	Yes	2	181	11.1	0	182	0.00	Dov to te	
13 14	Obesity							ynlo Supe	
15	No	598	48412	12.4	338	56737	5.96	2005 a (0.46, 0.60)***	0.57(0.50, 0.65)***
16 17	Yes	7	424	16.5	3	536	5.60	augg 3(0.10, 1.49)	0.40(0.14, 1.19)
18	Atrial fibrillation							ninii BES)	
19 20	No	576	46291	12.4	320	54553	5.87	1 .5 1 (0.45, 0.59)***	0.56(0.49, 0.64)***
21	Yes	29	2545	11.4	21	2720	7.72	a. 72 (0.41, 1.26)	0.70(0.38, 1.30)
22	Drugs used							vinin	
24	Oral steroid							g, ar	
25 26	No	318	17828	17.8	166	21844	7.60	3 0.4 3 (0.40, 0.58)***	0.53(0.44, 0.64)***
27	Yes	287	31008	9.26	175	35429	4.94	a.56(0.46, 0.68)***	0.59(0.49, 0.72)***
28 29	NSAID							- Jur	
30	No	216	7329	29.5	105	9509	11.0	J.44(0.37, 0.58)***	0.54(0.43, 0.69)***
31	Yes	389	41506	9.37	236	47764	4.94	a 0.5 8 (0.47, 0.64)***	0.56(0.48, 0.66)***
33	Statin							s. 25 at	
34 35	No	586	45820	12.8	322	54040	5.96	0.5 4 (0.44, 0.58)***	0.56(0.49, 0.64)***
36	Yes	19	3016	6.30	19	3233	5.88	0.9 a (0.50, 1.79)	0.97(0.49, 1.95)
37 38	Conventional							Bib	
39	DMARDS							liogr	
40 41	No	347	14099	24.6	181	18431	9.82	0.48(0.40, 0.57)***	0.54(0.45, 0.65)***
42	Yes	258	34736	7.43	160	38842	4.12	0.55(0.46, 0.68)***	0.58(0.47, 0.71)***
43 44	Biological DMARDs		For peer revie	ew only - http:	//bmjopen.bmj.c	om/site/abou	t/guidelines.xht	ml de	
45									
46									

No	591	44821	13.2	BMJ Ope 336	n 52599	6.39	a by b 3 (0.46, 0.60)***	Page 38 of 0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	b b b b b b c c c c c c c c c c	0.26(0.09, 0.80)**
Abbreviation: IR, i	incidence rate per	1,000 person	-years; SHR	, subhazard r	atio; CI, confi	dence interval	3-075 ght, i	<u>.</u>
Adjusted SHR: adj	justed for accepted	d acupuncture	e, age, sex, c	omorbidities,	and drugs use	ed in the comp	engerisks regression m	odels.
*• n < 0.05• **• n	< 0.01, *** n < 0.	001					on 1: ding	
$p < 0.03, \dots, p < \Delta$	$< 0.01, \cdots p < 0.0$	ammatory dru	ige (NSAID	s) DMARD	(disease-modit	fving antirheu	or π mesticedruge)	
		annihator y are	igs (115711D	<i>s)</i> , Dim itel	(uisease moun	i ying antimea	essa ssar	
							y 20; vigne	
							ed to	
							ownl t Sup	
							oade and	
							ed fro data	
							mini h	
							ng, /	
							bmjc	
							ining	
							y, an	
							com/	
							on	
							June	
							11, ;	
							2025 gies.	
							at A	
							genc	
							ë Bii	
							bliog	
							Iraph	
							nique	
		For peer revi	ew only - http	://bmjopen.bm	j.com/site/about	/guidelines.xhtr	ml e	

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

5		Rheumatoi			
6	1	Accepted ad			
7 Variable	No (n =	=22218)	Yes (n =	-12266)	difference
9	n	%	n	%	-
1 0 1 Gender					
¹² Women	16702	75.2	10109	82.4	0.18
13 14 Men	5516	24.8	2157	17.6	0.18
¹⁵ Age group					Prote
16 17 18-39	2994	13.5	1767	14.4	0.03 če
18 40-59	12351	55.6	7762	63.3	0.16 b
$_{20} \ge 60$	6873	30.9	2737	22.3	0.20 g
²¹ Mean±SD (years)	56.7	±14.7	54.3±	13.3	0.17 ⁿⁱ
22 2Baseline Comorbidity					ţ, j
²⁴ Diabetes mellitus	4117	18.5	2260	18.4	0.003 6
25 26 Hypertension	8857	39.9	4632	37.8	0.04 ^{bg}
²⁷ Hyperlipidemia	5610	25.3	3593	29.3	0.09 c
28 29 Congestive heart failure	1698	7.64	736	6.00	0.07 Ses
³⁰ Depression	1901	8.56	1394	11.4	0.09 relation
31 32 Anxiety	4591	20.7	3118	25.4	
³³ Alcoholism	422	1.90	244	1.99	0.01 text
34 35 Tobacco used	146	0.66	84	0.68	0.003 and a
³⁶ Obesity	188	0.85	163	1.33	0.05
37 Second	1102	4.96	845	6.89	а́а 0.08 Э Е
³⁹ Drug used					ining
40 Oral steroid	10814	48.7	6946	56.6	0.16 ≥
⁴² NSAID	13907	62.6	9532	77.7	0.34 ta
43 44 Statin	828	3.73	688	5.61	0.09 g
45 Conventional DMARDS					and
40 47 Hydroxychloroquine	9299	41.9	6059	49.4	0.15 s i
⁴⁸ Sulfasalazine	7210	32.5	4606	37.6	0.11 a r
50 Methotrexate	14	0.06	11	0.09	0.01 ^{fe}
51 Leflunomide	1309	5.89	973	7.93	0.08 D
52 53 D-penicillamine	196	0.88	138	1.13	0.02 gr
54 Azathioprine	385	1.73	229	1.87	0.01
56 Mycophenolate	10	0.05	7	0.06	0.01
57 Cyclosporine	816	3.67	594	4.84	0.06
59 59 59 59 59 59 59 59 59 59 50 59 50 50 50 50 50 50 50 50 50 50 50 50 50					

	BMJ Op	ben			Page 40 o
tanercept	941	4.24	706	5.76	0.07
dalimumab	345	1.55	202	1.65	0.01
es of acupuncture					
Ianual acupuncture			10604	86.45	
lectroacupuncture			407	3.32	
combination of manual acupuncture and					
troacupuncture			1255	10.23	
ation between rheumatoid arthritis date					
index, days (mean, median)	(981.29	9, 668.0)	(1047.36	5, 688.5)	
puncture visits, (mean, meidan)			(10.43	, 3.00)	
mean (median) of follow-up period were 4.9	96 (4.39) and	4.01 (3.17)	vears for act	ipuncture coh	ort and compared
ort	- ())	r	I I I I
nt.			(1)	- 1:C.:	
reviation: Nonsteroidal anti-inflammatory di	rugs (NSAIL	DS), DMARL	(disease-m	odifying antir	neumatic drugs).

¹₂Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted 3 acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in $\frac{4}{5}$ un-matching.

6 Variable	No. of event		Crude [*]			$\mathbf{Adjusted}^{\dagger}$	
7 variable 8	(n=1441)	SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
⁹ Accepted acupuncture							
10 11 No	1080	1.00	reference		1.00	reference	
12 Yes	361	0.48	(0.42, 0.53)	< 0.001	0.65	(0.58, 0.74)	< 0.001

¹Crude SHR^{*} represented relative subhazard ratio;

¹⁵ Adjusted SHR[†] represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, ¹⁷ ¹⁷ ¹⁸ ¹⁸

19	
19	
20	
21	
22	
23	
24	
25	
26	
20	
27	
28	
29	
30	
31	
32	
33	
34	
25	
35	
30	
37	
38	
39	
40	
41	
42	
/3	
45	
44	
45	
46	
47	
48	
49	
50	
51	
52	
52	
54	
55	
56	
57	
58	
59	
60	
00	

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.



Page 43 of 43

	ST	'ROBE 2007 (v4) Statement—Checklist of items that should be included in reports of chase a control studies	
Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(b) Provide in the abstract an informative and balanced summary of what was done and what a short and what because the stract and the stract and balanced summary of what was done and what because the stract and the stract and the stract and balanced summary of what was done and what because the stract and the stract and balanced summary of what was done and what because the stract and the stract and balanced summary of what was done and what because the stract and th	1-5
Introduction		2022 Inter	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods		an de rieiei	
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and contropselection. Give the rationale for the choice of cases and controls	9-10
		(b) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier diagnostic criteria, if	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how matching of cases and controls was addressed	11
		(e) Describe any sensitivity analyses	11
Results		Ŭ a	

 lographique de l

		BMJ Open by copyrig copyrig 2023	Page 44
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information စာကုန်စုံosures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their predstary (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningfu	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses B	13
Discussion		ning S) t	
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of a alyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information		ar on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine 🕉 rg/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.sepidem.com/).

BMJ Open

BMJ Open

The effect of acupuncture on ischemic stroke in patients with rheumatoid arthritis: A nationwide propensity scorematched study

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-075218.R3
Article Type:	Original research
Date Submitted by the Author:	09-Nov-2023
Complete List of Authors:	Huang, Chia-Yu; China Medical University, Huang, Ming-Cheng; China Medical University Hospital, Department of Chinese Medicine Liao, Hou-Hsun; China Medical University Lin, Cheng-Li; China Medical University Hospital; China Medical University Lee, Yu-Chen; China Medical University, Graduate Institute of Acupuncture Science; China Medical University Hospital, Acupuncture Department Zimmerman, Gregory; China Medical University Wu, Mei-Yao; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University Hospital, Department of Chinese Medicine; China Medical University
Primary Subject Heading :	Complementary medicine
Secondary Subject Heading:	Rheumatology, Neurology
Keywords:	Stroke < NEUROLOGY, COMPLEMENTARY MEDICINE, RHEUMATOLOGY

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

The effect of acupuncture on ischemic stroke in patients with rheumatoid arthritis: A nationwide propensity score-matched study **Authors:** Chia-Yu Huang, M.D., Ph.D.^{1,2†}, Ming-Cheng Huang, M.D., Ph.D.^{1,3†}, Hou-Hsun Liao, M.D., M.S.^{2,3}, Cheng-Li Lin, M.S.^{4,5}, Yu-Chen Lee, M.D., Ph.D.^{3,6}, Gregory Zimmerman, M.S.⁶, Mei-Yao Wu, M.D., Ph.D.^{3,7,8††}, Hung-Rong Yen, M.D., Ph.D.^{1,3,8,9,10,††} [†]Chia-Yu Huang and Ming-Cheng Huang contributed equally to this work and share first authorship. [†] Mei-Yao Wu and Hung-Rong Yen contributed equally to this work and share corresponding authorship. **Affiliations:** ¹Department of Family Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan ²Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan ³Department of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan ⁴Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan. ⁵College of Medicine, China Medical University, Taichung, Taiwan ⁶Graduate Institute of Acupuncture Science, College of Chinese Medicine, China Medical University

BMJ Open

1	⁷ School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine,
2	China Medical University, Taichung, Taiwan
3	⁸ Research Center for Traditional Chinese Medicine, Department of Medical Research,
4	China Medical University Hospital, Taichung, Taiwan
5	⁹ Chinese Medicine Research Center, China Medical University, Taichung, Taiwan
6	
7	Corresponding authors:
8	Hung-Rong Yen, M.D., Ph.D.
9	School of Chinese Medicine, College of Chinese Medicine, China Medical University,
10	Taichung, Taiwan
11	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
12	Tel. : +886-4-22053366 ext. 3313
13	Fax: +886-4-22365141
14	E-mail: hungrongyen@gmail.com
15	or
16	Mei-Yao Wu, M.D., Ph.D.
17	School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, China
18	Medical University, Taichung, Taiwan
19	91 Hsueh-Shih Rd, North District, Taichung 404, Taiwan
20	Tel. : +886-4-22052121 ext. 4561
21	Fax: +886-4-22365141
22	E-mail: meiyaowu0919@gmail.com
23	
24	E-mail addresses for all authors:
25	Chia-Yu Huang: dochuangcharlie@gmail.com
26	Ming-Cheng Huang: mchuang1128@gmail.com

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Hou-Hsun Liao: a202098@cmu.edu.tw

2	
3 4 5	1
5 6 7	2
, 8 9	3
10 11	4
12 13	5
14 15	6
16 17 19	7
18 19 20	8
21 22	9
23 24	10
25 26	-0
27 28	10
29 30	12
31 32	13
33 34	14
35 36	15
37 38 30	16
39 40 41	17
42	18
44 45	19
46 47	20
48 49	21
50 51	22
52 53	23
54 55 56	24
50 57 58	25
59 60	26

Cheng-Li Lin: orangechengli@gmail.com				
Yu-Chen Lee: d5167@mail.cmuh.org.tw				
Gregory Zimmerman: gregzlac@gmail.com				
Mei-Yao Wu: meiyaowu0919@gmail.com				
Hung-Rong Yen: hungrongyen@mail.cmu.edu.tw				
Running title: Acupuncture Reduced the Risk of Stroke				
Word count: Abstract: 275; Text: 2490; No of tables: 1; No of figures: 2				
Keywords: Acupuncture; Cardiovascular diseases; National Health Insura	ance			
Research Database; Rheumatoid arthritis; Stroke				

1 2						
- 3 4	1	Abstract				
5 6 7	2	Objectives: The purpose of this study was to demonstrate that acupuncture is				
8 9	3 beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheuma					
10 11	4	arthritis (RA).				
12 13 14	5	Design: This is a propensity score-matched cohort study.				
15 16	6	Setting: This is a nationwide population-based study.				
17 18	7	Participants: Patients with RA diagnosed between January 1, 1997, and December				
19 20 21	8	31, 2010, through the National Health Insurance Research Database				
22 23	9	Interventions: The patients who were administered acupuncture therapy from the				
24 25	10	initial date of RA diagnosis of rheumatoid arthritis to December 31, 2010, were				
26 27	11	included in the acupuncture cohort. Patients who did not receive acupuncture				
28 29 30	12	treatment during the same time interval constituted the no-acupuncture cohort.				
31 32	13	Primary outcome measures: A Cox regression model was used to adjust for age, sex,				
33 34	14	comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of				
35 36 27	15	IS between these two cohorts through competing-risks regression models.				
37 38 39	16	Results: After 1:1 propensity score matching, a total of 23,226 patients were				
40 41	17	identified. The basic characteristics of these patients were similar. A lower cumulative				
42 43	18	incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, p $<$				
44 45 46	19	0.001; immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the				
47 48	20	end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605				
49 50	21	patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced				
51 52	22	ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering				
55 55	23	ischemic stroke incidence through acupuncture therapy in RA patients was				
56 57	24	independent of sex, age, types of drugs used, and comorbidities.				
58 59	25	Conclusions: This study showed the beneficial effect of acupuncture in reducing the				
60	26	incidence of ischemic stroke in patients with RA.				

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
20 27	
27	
20	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40 41	
41 42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53 F1	
54	
55 56	
57	
58	
59	
60	

5

1 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 ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.

• The causality could not be proven directly through our study design.

	/	
	8	
	9	
1	.0	
1	.1	
1	.2	
1	.3	
1	4	
1	.5	
1	.6	
1	.7	
1	.8	
1	9	
2	20	
2	21	
2	22	
2	23	
2	24	
2	25	
2	26	r.
		5
1 Introduction

Rheumatoid arthritis (RA) is a common rheumatoid disease that manifests as polyarthritis 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 diseases (CVDs) [2-5]. Comorbidities from CVD, such as stroke, are the major cause of death in RA patients [6-11]. Compared to 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 ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar to that in Caucasian populations (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue for clinical doctors and patients [18]. The common prescriptions to treat RA are nonsteroidal 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 (MTX) and infliximab, have advantages in the prevention of ischemic 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.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

In many countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA [21-25]. A previous cohort

BMJ Open

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 hypothesized 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 ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is 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 ischemic stroke prevention in patients with RA who accepted acupuncture treatment.

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 a 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 (CMUH104-REC2-115).

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

21 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 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with a diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) as follows: 1) patients who were younger than 18 years;

BMJ Open

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

> 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 ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 newly diagnosed RA patients were included. Patients who received acupuncture therapy from the initial RA diagnosis to December 31, 2010, were included in the acupuncture cohort (n=12,266). We used a propensity score approach to minimize 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 (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401-405), hyperlipidemia (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),

BMJ Open

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 ischemic stroke (ICD-9-CM: 433-438)
were compared between the acupuncture and nonacupuncture cohorts of RA patients.

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].

12 Statistical analyses

The standardized 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 less than 0.1 standard deviation (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 ischemic 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.

- 25 Patient and Public Involvement
 - 26 None

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 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 enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and nonacupuncture cohort (Fig. 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 HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. 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, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (Supplementary Table 1). The incidence of ischemic stroke in RA patients increased with age, with older patients having a higher risk. The adjusted SHRs in the 40–59-year-old group and the over 60-year-old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

BMJ Open

cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, p < 0.001, Fig. 2).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the nonacupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50-0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). Patients in the age subgroup ≥ 40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44-0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic 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 nonmatching analysis were also provided to prevent possible sampling bias from our 1:1 propensity score matching in Supplementary Tables 3 and 4. The final results analyzed by competing-risk regression models are compatible with the results after 1:1 propensity score matching.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

1 Discussion

To the best of our knowledge, this is the first study to show that acupuncture therapy is beneficial for ischemic 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 ischemic 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 CVD 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 CVD risk in RA [37]. Therefore, it is interesting to know whether acupuncture fits the niche to reduce inflammation in RA patients.

There is some evidence and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] 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

BMJ Open

studies, acupuncture reduced inflammation in a collagen-induced arthritis model [44-46]. Furthermore, acupuncture not only has analgesic effects through beta-endorphin [47], adenosine [48] 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 ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [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 had 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 minimized. 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 minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic 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 wishes of the patients. Because of the standard TCM program

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Page 16 of 43

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

> training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (Supplementary Fig. 1) [55,56]. Further clinical trials with standardized 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.

8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	15
	15

1 Conclusions

Our study demonstrates that the ischemic 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 ischemic stroke. The study also offers important ideas for more comprehensive research in the future.

8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
	16

BMJ Open

Ethics Approval Statement

The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

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.

Funding

This work was financially supported by the "Chinese Medicine Research Center, China Medical University" from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-1). This study was also supported in part by China Medical University (CMU103-BC-4-2, CMU105-BC-1-1, CMU105-BC-1-2), China Medical University Hospital (DMR-107-011, DMR-110-002, and DMR-111-105), and the Ministry of Science and Technology (MOST108-2638-B-039-001-MY2, MOST107-2320-B-039-037, MOST108-2320-B-039-021, and MOST110-2321-B-

039-003). This study is also supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW111-TDU-B-212-134004), Taiwan. None of the funders and institutions listed had a role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Acknowledgment

This study was based in part on data from the National Health Insurance Research

BMJ Open

 Database, provided by the National Health Insurance Administration, Ministry of
 Health and Welfare, and managed by National Health Research Institutes. The
 interpretation and conclusions contained herein do not represent those of the National
 Health Insurance Administration, Ministry of Health and Welfare, or National Health
 Research Institutes.

7 Authors' contributions

CYH and MCH contributed equally. 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 finalized the manuscript. MYW and HRY contributed equally as cocorresponding authors.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

20 Data availability

- 21 The datasets generated during and/or analyzed during the current study are available
- 22 from the corresponding author upon reasonable request.

References

- Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990; 16:513-37.
- Sesin CA, Bingham CO, 3rd. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2005;35:185-196.
- 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 Jun* 2008;15:762-784.
 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;69:1010-1014.
- 5. Smolen JS, Landewe 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;69:964-975.
- 6. Avina-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;59:1690-1697.
- 7. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular

BMJ Open

events in patients with rheumatoid arthritis: a meta-analysis of observational studies.
Ann Rheum Dis 2012;71:1524-1529.
8. de Groot L, Posthumus MD, Kallenberg CG, et al. Risk factors and early detection
of atherosclerosis in rheumatoid arthritis. Eur J Clin Invest 2010;40:835-842.
9. Meune C, Touze E, Trinquart 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;103:253-261.
10. Peters MJ, Symmons DP, 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;69:325-331.
11. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best
Pract Res Clin Rheumatol 2011;25:469-483.
12. 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;59:1090-1096.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

13. 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;41:863-877.

- 14. 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;33:248-255
- 15. Lai CH, Lai MS, Lai KL, et al. Nationwide population-based epidemiologic study of rheumatoid arthritis in Taiwan. *Clin Exp Rheumatol* 2012;30:358-363.
- 16. Liou TH, Huang SW, Lin JW, 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* 20113;72:541-546.
- Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. *Curr Treat Options Neurol* 2015;17:356.
- 19. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591-2602.
- 20. Bowman SJ. Hematological manifestations of rheumatoid arthritis. *Scand J Rheumatol* 2002;31:251-259.
- 21. Seca S, Patricio M, Kirch S, et al. Effectiveness of Acupuncture on Pain,

3
4
5
6
7
, Q
0
9
10
11
12
13
14
15
16
17
18
19
20
21
27
∠∠ ??
23
24
25
26
27
28
29
30
31
32
33
34
35
36
50 27
3/
38
39
40
41
42
43
44
45
46
47
48
49
50
51
57
52 52
55 54
54
55
56
57
58
59
60

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.

- 22. Tam LS, Leung PC, Li TK, et al. Acupuncture in the treatment of rheumatoid arthritis: a double-blind controlled pilot study. *BMC Complement Altern Med* 2007;7:35.
- 23. 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;15:187-193.
- 24. Chou PC, Chu HY. Clinical Efficacy of Acupuncture on Rheumatoid Arthritis and Associated Mechanisms: A Systemic Review. *Evid Based Complement Alternat Med* 2018;8596918.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

25. Huang CY, Wu MY, Huang MC, 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;14:1-9.
26. Huang MC, Pai FT, Lin CC, 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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

3
4
5
6
0
/
8
9
10
11
12
13
14
15
16
10
17
18
19
20
21
22
23
23
24
25
26
27
28
29
30
31
32
33
31
24 27
35
36
37
38
39
40
41
42
<u>4</u> 2
43
44
45
46
47
48
49
50
51
52
52
52
54
55
56
57
58
59
60

1 2

> 27. Shih CC, Liao CC, Sun MF, et al. A Retrospective Cohort Study Comparing Stroke Recurrence Rate in Ischemic Stroke Patients With and Without Acupuncture Treatment. *Medicine (Baltimore)* 2015;94:e1572.

> 28. Huang CY, Wu MY, Chang CL, 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;63:1-9.

29. Huang CY, Wu MY, Kuo YH, 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.

30. Wu MY, Huang MC, Liao HH, 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.

31.Wu MY, Lee YC, Lin CL, 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.

32. 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*

2	
3	
4	2017;76:17-28.
5	
6	
7	33 Karpouzas GA Ormseth SR Hernandez E et al Impact of Cumulative
8	
9	
10	Inflammation Cardiac Risk Factors and Medication Exposure on Coronary
11	initialinitation, Cardiae Nisk I actors, and Wedleation Exposure on Coronary
12	
13	Athorogalarogic Prograssian in Phaymatoid Arthritic Arthritic Phaymatol
14	Autoroscierosis Progression in Kileumatolu Artinitus. Artinitus Kileumator
15	
16	2020.72.400 409
17	2020;72:400-408.
18	
10	
20	34. Visvanathan S, Rahman MU, Keystone E, et al. Association of serum markers
20	
21	
22	with improvement in clinical response measures after treatment with golimumab in
23	
24	
25	patients with active rheumatoid arthritis despite receiving methotrexate: results
26	
27	
28	from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.
29	
30	
31	35 Kleinert S Tony HP Krause A et al Impact of national disease characteristics
32	set filometes, fong fil, filouse fi, et un impact of panent and abouse enalacteristics
33	
34	on the range tic success during adaligning treatment of natients with rheumatoid
35	on therapeutie success during adaminantab treatment of patients with meanatola
36	
37	arthritic: data from a German noninterventional observational study. <i>Phaumatal Int</i>
38	artifittis. data from a Ociman nominer ventional observational study. <i>Kneumuloi mi</i>
39	
40	2012.22.2750.2767
41	2012,52.2759-2767.
42	
42	
45	36. Wijbrandts CA, Dijkgraaf MG, Kraan MC, et al. The clinical response to
44	
45	
40	infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour
47	
48	
49	necrosis factor alpha expression in the synovium. Ann Rheum Dis
50	
51	
52	2008;67:1139-1144.
53	
54	
55	37. Karpouzas GA, Ormseth SR, Hernandez E, et al. Biologics may prevent
56	1 ····································
57	
58	cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque
59	carate rassular events in meanatora arannas by minorang coronary plaque
60	
	24

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

formation and stabilizing high-risk lesions. *Arthritis Rheumatol* 2020;72, 1467-1475.

- 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;177:508-515.
 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;179:1388-1397.

- 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;27:103-105.
- 42. Lee H, Lee JY, Kim YJ, et al. Acupuncture for symptom management of rheumatoid arthritis: a pilot study. *Clin Rheumatol* 2008;27:641-645.
- 43. Ouyang BS, Gao J, Che JL, 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;17:505-509.
 44. He X, Huang L, Qiu S, et al. beta-Endorphin attenuates collagen-induced arthritis

BMJ Open

partially by inhibiting peripheral pro-inflammatory mediators. Exp Ther Med
2018;15:4014-4018.
45. Ye TS, Du ZH, Li ZH, et al. Repeated Electroacupuncture Persistently Elevates
Adenosine and Ameliorates Collagen-Induced Arthritis in Rats. Evid Based
Complement Alternat Med 2016;3632168.
46. Li J, Li J, Chen R, et al. Targeting NF-kappaBeta 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;13:883-888.
49. Chen YH, Lee HJ, Lee MT, et al. Median nerve stimulation induces analgesia via
orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. Proc
<i>Natl Acad Sci U S A</i> 2018;115:E10720-E9.
50. Torres-Rosas R, Yehia G, Pena G, et al. Dopamine mediates vagal modulation of
the immune system by electroacupuncture. Nat Med 2014;20:291-295.
51. Hsieh CH. The effects of auricular acupressure on weight loss and serum lipid
levels in overweight adolescents. Am J Chin Med 2010;38:675-682.
26

52. Flachskampf FA, Gallasch J, Gefeller O, et al. Randomized trial of acupuncture	to .
lower blood pressure. Circulation 2007;115:3121-3129.	
53. Semb AG, Ikdahl E, Wibetoe G, et al. Atherosclerotic cardiovascular disease	
prevention in rheumatoid arthritis. Nat Rev Rheumatol 2020;16:361-379.	P
54. Rassen JA, Shelat A.A, Myers J, et al. One-to-many propensity score matching i	n cted
cohort studies. <i>Pharmacoepidemiol Drug Saf</i> 2012;21:69-80.	by соруг
55. Tou SI, Huang CY, Yen HR. Effect of Acupoint Stimulation on Controlling Pair	ight, inc
from Heel Lance in Neonates: A Systematic Review and Meta-Analysis of	luding fc
Randomized Controlled Trials. Children 2023;10:1024.	Ensei uses r
56. Lin JG, Li TM, Hsu SF. Newly Edited Color Book of Acupuncture and	gnement blated to
Moxibustion; JYIN Publishing Company: Taipei, Taiwan, 2009.	: Superie text and
	ur (ABE: data mi
	s) ning, Al
	training
	, and sim
	nilar tech
	nologies
	ç,
27	-
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

	R	Rheumatoid Arthritis					
Variabla	Ac	upunctu	re treatme	ent	Standardized mean difference		
v al lable	No (n =	= 11613)	Yes (n =	11613)			
	n	%	n	%			
Sex							
Women	9499	81.8	9478	81.6	0.01		
Men	2114	18.2	2135	18.4	0.01		
Age group							
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 \pm 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		
Hyperlipidemia	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		

Table 1. Characteristics of rheumatoid arthritis patients according to whether they

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Cvclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid					
arthritis diagnosis and index,	(1078.52	2, 795.0)	(1065.18	, 707.0)	0.32
days (mean, median)					
Acupuncture visits (mean,		-	(9.83, 2	3.00)	
median)					

The mean (median) follow-up periods were 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviations: nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD

(disease-modifying antirheumatic drugs)

Figure legends

Fig. 1. Study population flowchart

A total of 47,809 patients with rheumatoid arthritis 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

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











Fig. 2

170x164mm (96 x 96 DPI)

BMJ Open 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.

	No. of	No. of Crude [*]			-075; ht, in	Adjusted [†]		
Variable	event (n = 946)	SHR	(95% CI)	p-value	218 on 1 Slang	(95% CI)	p-value	
Acupuncture treatment					3 Fei for u			
No	605	1.00	reference		1 Sobs Tra	reference		
Yes	341	0.52	(0.46, 0.60)	< 0.001		(0.49, 0.65)	< 0.001	
Sex					024. ted t			
Women	714	1.00	reference			reference		
Men	231	1.44	(1.24, 1.67)	< 0.001		(1.14, 1.54)	< 0.001	
Age group					ided id da			
18-39	13	1.00	reference		1 \$ 0 \$ 5	reference		
40-59	372	7.17	(4.14, 12.4)	< 0.001		(3.44, 10.4)	< 0.001	
≥ 60	561	28.1	(16.3, 48.6)	< 0.001	1 9 .7	(8.38, 25.7)	< 0.001	
Baseline Comorbidity					ul tra			
(ref = no comorbidity)					ining			
Diabetes mellitus	334	2.64	(2.31, 3.01)	< 0.001	ျမ္မာ8	(1.36, 1.82)	< 0.001	
Hypertension	654	3.96	(3.45, 4.54)	< 0.001	2 2 2 0 S	(1.79, 2.47)	< 0.001	
Hyperlipidemia	371	1.94	(1.70, 2.21)	< 0.001		(0.93, 1.25)	0.30	
Congestive heart failure	148	3.18	(2.67, 3.79)	< 0.001	ן 1 פ ון 1	(1.08, 1.59)	0.006	
Depression	120	1.46	(1.21, 1.77)	< 0.001	1012 1	(0.91, 1.37)	0.28	
Anxiety	256	1.40	(1.21, 1.61)	< 0.001	0°°°99'28	(0.85, 1.16)	0.94	
Alcoholism	20	1.48	(0.95, 2.29)	0.08	ອ 1.46 ຊ	(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 e	(0.58, 2.08)	0.77	
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89 <mark>B</mark>	(0.66, 1.19)	0.43	
Drugs used					iogr			
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51 <mark>ap</mark>	(0.42-0.62)	< 0.0001	
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24 g	(0.11-0.51)	0.0002	
Statin	329 For p	eer review 1.04	only - http://bmjopen.bmj.com (0.92-1.17)	/site/about/guideline 0.5575	es.xhtml 0.65 e	(0.58-0.74)	< 0.0001	

Page 35 of 43	Conventional DMARDS			BMJ Open		ıjopen I by co		
	Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001	PV 7702	(0.60, 0.81)	< 0.001
1 2	Sulfasalazine	235	0.47	(0.41, 0.54)	< 0.001	0.80 5.07	(0.68, 0.94)	0.007
3	Methotrexate	2	1.88	(0.50, 7.04)	0.35	יים 2 18 31 <u>1</u> 5	(0.84, 11.9)	0.08
4 5	Leflunomide	18	0.22	(0.14, 0.35)	< 0.001		(0.22, 0.54)	< 0.001
6	D-penicillamine	11	0.85	(0.46, 1.53)	0.53		(0.61, 1.88)	0.05
7 8	Azathioprine	9	0.39	(0.20, 0.75)	0.004		(0.40, 1.49)	0.44
9	Mycophenolate	0	-	-		ary 2 seigi s rela	-	
10 11	Cyclosporine	35	0.62	(0.44, 0.87)	0.005		(0.99, 1.98)	0.06
12	Biological DMARDs					ent of to to		
13 14	Etanercept	16	0.27	(0.16, 0.44)	< 0.001		(0.31, 0.83)	0.007
15	Adalimumab	3	0.18	(0.06, 0.57)	0.003	not a dec	(0.14, 1.34)	0.15
16 17	Conventional DMARDS					d fro r (AE ata I		
18	Hydroxychloroquine	333	0.47	(0.41, 0.54)	< 0.001		(0.60, 0.81)	< 0.001
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	competing-risks regression mo Abbreviation: Nonsteroidal an	odels. ti-inflamma	tory drugs (N	/ - http://bmjopen.bmj.com/	ase-modifying anti	aining, ago anno 11, 2025 at Agence Bibliographique de l irheunand similar technologies.	gs).	

BMJ Open Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke Brite umatoid 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			Rheum	$\stackrel{\mathfrak{R}}{=}$ Scompared with no	Compared with non-acupuncture users				
	No				Yes		Crude SHR	Adjusted SHR	
		(n = 11613)			(n = 11613)		on 1: ding		
	Event	Person years	\mathbf{IR}^{\dagger}	Event	Person years	\mathbf{IR}^\dagger	or Fe (95% CI)	(95% CI)	
							uary es re		
Total	605	48836	12.4	341	57273	5.95	a b c (0.46, 0.60)***	0.57(0.50, 0.65)***	
Sex							1. Do		
Women	460	40274	11.4	254	46907	5.41	D <u> 1</u> (0.44, 0.60)***	0.58(0.49, 0.67)***	
Men	145	8562	16.9	87	10366	8.39	a) (0.42, 0.71)***	0.54(0.41, 0.70)***	
Age group							ed fr ur (A data		
18-39	5	8734	0.57	8	8576	0.93	到 第 (0.49, 4.45)	1.45(0.44, 4.76)	
40-59	226	29529	7.65	146	37225	3.92	0.56 (0.43, 0.66)***	0.54(0.44, 0.66)***	
≥ 60	374	10573	35.4	187	11472	16.3	₹0.5 ⁵ (0.46, 0.65)***	0.58(0.48, 0.69)***	
Baseline Comorbidity							jope		
Diabetes mellitus							ng,		
No	383	41083	9.32	229	48060	4.76	a).55(0.47, 0.65)***	0.60(0.51, 0.71)***	
Yes	222	7753	28.6	112	9213	12.2	s 0.4 7 (0.38, 0.59)***	0.52(0.41, 0.65)***	
Hypertension							on Ju		
No	184	32174	5.72	108	37634	2.87	g.5a (0.41, 0.66)***	0.57(0.45, 0.72)***	
Yes	421	16661	25.3	233	19639	11.9 -	g).53(0.45, 0.62)***	0.57(0.49, 0.67)***	
Hyperlipidemia							025 Jies.		
No	366	36970	9.90	209	43496	4.81	0.5 ³ (0.45, 0.62)***	0.61(0.51, 0.72)***	
Yes	239	11866	20.1	132	13777	9.58	0.5 ³ (0.41, 0.63)***	0.51(0.41, 0.63)***	
Congestive heart							ё В		
failure							blio		
No	513	46595	11.0	285	54590	5.22	0.5 8 (0.44, 0.59)***	0.55(0.47, 0.64)***	
Yes	92	2241	41.1	56	2683	20.9	0.6 [±] (0.44, 0.85)***	0.65(0.47, 0.92)***	
Depression		For peer review	only - httr)://bmjopen.h	mi.com/site/about/o	uidelines.xh	tml C		
No	523	44638	11.7	303	52396	5.78	$0.5\overline{4}(0.47, 0.62)^{***}$	0.59(0.51, 0.67)***	

								njo	
Page 37 of 43	Yes	82	4198	19.5	BMJ Open 38	4877	7.79	a 0.4 3 (0.30, 0.64)***	0.48(0.32, 0.72)***
1	Anxiety							2023 Syrig	
2	No	442	38718	11.4	248	46073	5.38	<u>-</u> 0.5 % (0.44, 0.60)***	0.56(0.48, 0.66)***
3	Yes	163	10117	16.1	93	11200	8.30	2 0.5 2 (0.43, 0.71)***	0.57(0.44, 0.74)***
4 5	Alcoholism							on 1 ding	
6	No	596	48177	12.4	330	56529	5.84	q).5 ; (0.45, 0.59)***	0.56(0.49, 0.64)***
8	Yes	9	659	13.7	11	744	14.8	us my 1.12(0.47, 2.67)	1.25(0.50, 3.09)
9	Tobacco use							s rela	
10	No	603	48655	12.4	341	57090	5.97	a) 5 2 (0.46, 0.60)***	0.57(0.50, 0.65)***
12	Yes	2	181	11.1	0	182	0.00	Dov to te	
13 14	Obesity							vnlo supe	
15	No	598	48412	12.4	338	56737	5.96	Des a (0.46, 0.60)***	0.57(0.50, 0.65)***
16 17	Yes	7	424	16.5	3	536	5.60	a) a (0.10, 1.49)	0.40(0.14, 1.19)
18	Atrial fibrillation							m ht BES)	
19 20	No	576	46291	12.4	320	54553	5.87	0.5	0.56(0.49, 0.64)***
21	Yes	29	2545	11.4	21	2720	7.72	f. 72 (0.41, 1.26)	0.70(0.38, 1.30)
22 23	Drugs used							inin n	
24	Oral steroid							g, an	
25 26	No	318	17828	17.8	166	21844	7.60	a).48(0.40, 0.58)***	0.53(0.44, 0.64)***
27	Yes	287	31008	9.26	175	35429	4.94	a).56(0.46, 0.68)***	0.59(0.49, 0.72)***
28 29	NSAID							Jun	
30	No	216	7329	29.5	105	9509	11.0	a.44(0.37, 0.58)***	0.54(0.43, 0.69)***
31	Yes	389	41506	9.37	236	47764	4.94	a).5 8 (0.47, 0.64)***	0.56(0.48, 0.66)***
33	Statin							s. 15 at	
34 35	No	586	45820	12.8	322	54040	5.96	0.5% (0.44, 0.58)***	0.56(0.49, 0.64)***
36	Yes	19	3016	6.30	19	3233	5.88	0.9a) (0.50, 1.79)	0.97(0.49, 1.95)
37 38	Conventional							Bib	
39	DMARDS							liogr	
40 41	No	347	14099	24.6	181	18431	9.82	0.43(0.40, 0.57)***	0.54(0.45, 0.65)***
42	Yes	258	34736	7.43	160	38842	4.12	0.5 5 (0.46, 0.68)***	0.58(0.47, 0.71)***
43 44	Biological DMARDs		For peer revie	ew only - http:	://bmjopen.bmj.c	om/site/abou	t/guidelines.xht	ml de	
45									
40									

No	591	44821	13.2	BMJ Ope 336	n 52599	6.39	by b 3 . 5 . 5 . 5 . 5 . 5 . 5 . 5 . 5	Page 38 of 0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	b b b b b b c c c c c c c c c c	0.26(0.09, 0.80)**
Abbreviation: IR, i	incidence rate per	1,000 person	-years; SHR	, subhazard r	atio; CI, confi	dence interval	3-075 ght, i	<u> </u>
Adjusted SHR: adj	justed for accepted	d acupuncture	e, age, sex, c	omorbidities,	and drugs use	ed in the comp	eengerisks regression m	odels.
*• n < 0.05• **• n	< 0.01, *** n < 0.	001					on 1: ding	
$p < 0.03, \dots, p < \Delta$	$< 0.01, \cdots p < 0.0$	ammatory dru	ige (NSAID	s) DMARD ((disease-modit	fving antirheu	or π mesticedruge)	
		annihator y are	igs (115711D	<i>s)</i> , Dim itel ((ulseuse moul	i ying antimea	essa ssar	
							y 20; vigne	
							ed to	
							ownl t Sup	
							oade and	
							ed fro data	
							mini h	
							ng, /	
							bmjc	
							ining	
							y, an	
							com/	
							on	
							June	
							11, ;	
							2025 gies.	
							at A	
							genc	
							ë Bii	
							bliog	
							Iraph	
							nique	
		For peer revi	ew only - http	://bmjopen.bmj	j.com/site/about	/guidelines.xhtr	ml e	

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

5		Rheumatoi			
6		Accepted ad			
7 Variable	No (n =	=22218)	Yes (n =	=12266)	difference
9	n	%	n	%	_
1 0 1 Gender					
¹² Women	16702	75.2	10109	82.4	0.18
13 14 Men	5516	24.8	2157	17.6	0.18
¹⁵ Age group					Prote
16 17 18-39	2994	13.5	1767	14.4	0.03 če
18 40-59	12351	55.6	7762	63.3	0.16 by
$_{20}^{19} \ge 60$	6873	30.9	2737	22.3	0.20 g
²¹ Mean±SD (years)	56.7	±14.7	54.3±	13.3	0.17 ⁿⁱ
22 2Baseline Comorbidity					ţ, j
²⁴ Diabetes mellitus	4117	18.5	2260	18.4	0.003 c
25 26 Hypertension	8857	39.9	4632	37.8	
²⁷ Hyperlipidemia	5610	25.3	3593	29.3	0.09 c
28 29 Congestive heart failure	1698	7.64	736	6.00	0.07 Ses
³⁰ Depression	1901	8.56	1394	11.4	0.09 relation
31 32 Anxiety	4591	20.7	3118	25.4	
³³ Alcoholism	422	1.90	244	1.99	0.01 text
34 35 Tobacco used	146	0.66	84	0.68	0.003 and a
³⁶ Obesity	188	0.85	163	1.33	0.05 deur
37 Atrial fibrillation	1102	4.96	845	6.89	د ه H E 0.08
³⁹ ↓ Drug used					ining
40 Oral steroid	10814	48.7	6946	56.6	0.16 Ž
⁴² NSAID	13907	62.6	9532	77.7	0.34 ta i
45 44 Statin	828	3.73	688	5.61	0.09 g
45 AConventional DMARDS					and
40 47 Hydroxychloroquine	9299	41.9	6059	49.4	0.15 S
⁴⁸ Sulfasalazine	7210	32.5	4606	37.6	0.11 Tar
50 Methotrexate	14	0.06	11	0.09	0.01 E
⁵¹ Leflunomide	1309	5.89	973	7.93	0.08
53 D-penicillamine	196	0.88	138	1.13	0.02 gies
54 Azathioprine	385	1.73	229	1.87	0.01
56 Mycophenolate	10	0.05	7	0.06	0.01
57 Cyclosporine	816	3.67	594	4.84	0.06
598iological DMARDs					

	BMJ Op	ben			Page 40 o	
anercept	941	4.24	706	5.76	0.07	
dalimumab	345	1.55	202	1.65	0.01	
es of acupuncture						
anual acupuncture			10604	86.45		
ectroacupuncture			407	3.32		
ombination of manual acupuncture and						
roacupuncture			1255	10.23		
ation between rheumatoid arthritis date						
index, davs (mean, median)	(981.29	9, 668.0)	(1047.36	5, 688.5)		
puncture visits, (mean, meidan)			(10.43	, 3.00)		
mean (median) of follow-up period were 4	96 (4 39) and	4 01 (3 17)	vears for act	inuncture coh	ort and compared	
	, , , , , , , , , , , , , , , , , , ,		jeurs for uet	"puncture con	ore and compared	
ort.						
reviation: Nonsteroidal anti-inflammatory d	rugs (NSAIE	Ds), DMARE	O (disease-m	odifying antirl	heumatic drugs).	

¹₂Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted 3 acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in $\frac{4}{5}$ un-matching.

6 Nordahla	No. of event	$\mathbf{Adjusted}^{\dagger}$					
7 variable 8	(n=1441)	SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
⁹ Accepted acupuncture							
10 11 No	1080	1.00	reference		1.00	reference	
12 Yes	361	0.48	(0.42, 0.53)	< 0.001	0.65	(0.58, 0.74)	< 0.001

¹Crude SHR^{*} represented relative subhazard ratio;

¹⁵ Adjusted SHR[†] represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, ¹⁷ ¹⁷ ¹⁸ ¹⁸

19	
19	
20	
21	
22	
23	
24	
25	
26	
20	
27	
28	
29	
30	
31	
32	
33	
34	
25	
35	
30	
3/	
38	
39	
40	
41	
42	
43	
45	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
55	
54 55	
55	
56	
57	
58	
59	
60	

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open


Page 43 of 43

로 승 STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cerese control studies 은 없					
Section/Topic	ltem #	Recommendation	Reported on page #		
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-5		
		(b) Provide in the abstract an informative and balanced summary of what was done and what 🛪 🖧 und	1-5		
Introduction		2022 Inen Iateo			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8		
Objectives	3	State specific objectives, including any prespecified hypotheses	8		
Methods		and eriede			
Study design	4	Present key elements of study design early in the paper	9		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure	9-10		
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and contropselection. Give the rationale for the choice of cases and controls	9-10		
		(b) For matched studies, give matching criteria and the number of controls per case	9-10		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier diagnostic criteria, if	10-11		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10		
Bias	9	Describe any efforts to address potential sources of bias	9-10		
Study size	10	Explain how the study size was arrived at	9-10		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11		
		(b) Describe any methods used to examine subgroups and interactions	11		
		(c) Explain how missing data were addressed	11		
		(d) If applicable, explain how matching of cases and controls was addressed	11		
		(e) Describe any sensitivity analyses	11		
Results		ğ			

		BMJ Open by copyrig copyrig 2023	Page 44
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information စာကုန်စုံosures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their predstary (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningfu	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses B	13
Discussion		ning S) t	
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of a alyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information		ar on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine 🕉 rg/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.sepidem.com/).

lographique de l