

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The effect of acupuncture on ischemic stroke in patients with rheumatoid arthritis: A nationwide propensity score-matched study
<b>AUTHORS</b>	Huang, Chia-Yu; Huang, Ming-Cheng; Liao, Hou-Hsun; Lin, Cheng-Li; Lee, Yu-Chen; Zimmerman, Gregory; Wu, Mei-Yao; Yen, Hung-Rong

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Quah-Smith, I University of New South Wales
<b>REVIEW RETURNED</b>	04-Jul-2023

<b>GENERAL COMMENTS</b>	<p>It is mentioned that the first acupuncture intervention is average 1065 days after the rheumatoid arthritis (RA) - that is a rather long time. About 3 years?</p> <p>Was there a subset of data where the acupuncture intervention was much earlier, for example in the first 3 months-6 months before chronicity set in?</p> <p>This would have been interesting- as if the outcomes were even better, it may mean public health policy may change to include acupuncture in the protocol for RA management. Especially if it reduces the health dollar costs to the individual and the community.</p> <p>Electroacupuncture (EA) has sometimes been considered better than manual acupuncture- particularly in pain conditions. Comments please. Also why was there only such a small percentage of EA in the sample.</p> <p>It was stated the standard acupuncture points were used mostly. It would be good to state them eg LI11, ST36, SP9 - whatever selected, as well as having a pictorial / image with the most commonly used points for the readers who are not familiar with acupuncture and its acupoint locations on the body.</p> <p>Please comment about the 10 sessions which was the most common number required for positive change. Is this a biological turning point for acupuncture interventions?</p> <p>Were the sessions weekly or 2 x a week or a gradual change in frequency. Would increased frequency say from weekly to 2 x a week help in fast tracking reducing the inflammatory state. Please comment.</p> <p>Minor English spelling errors for example: Page 8 Line14 stroke - the spelling Page 9 Line3 and line 5- stroke- the spelling. Please check thoroughly.</p>
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<b>REVIEWER</b>	Wong, Wendy Chinese University of Hong Kong Chung Chi College, The Chinese University of Hong Kong
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REVIEW RETURNED	01-Aug-2023
GENERAL COMMENTS	<p>In a national wide proposal, this study aims at exploring the benefits of acupuncture for decreasing ischemic stroke in rheumatoid arthritis patients. In pragmatic reality, multi-morbidity has been increasing complicated and it is essential to have public health information to inform public policy for chronic disease management. In a cultural perspective, WHO had published the Traditional Medicine Strategy from 2002 to 2025 and therefore, acupuncture on this issue had become a very important topic to the health of Chinese.</p> <p>Abstract: As the major finding of the study had identified the number of acupuncture and duration for prevention of Ischemic stroke in this subset of RA patients. The outcomes should explicitly show this results.</p> <p>Background:</p> <p>1) There is a similar study that had published in 2018 in a national wide cohort, what is the difference between this publication with the previous one with coronary heart disease or ischemic stroke. 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.</p> <p>2) What is the TCM types (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 stands for?</p> <p>3) Patients group, intervention, control and outcomes were clearly defined in this cross-sectional study</p> <p>4) Why propensity score of 1:1 were used, please justify this?</p> <p>Results</p> <p>1) 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. This should be highlighted in the abstract.</p> <p>Discussion</p> <p>1) The application of this results with the year 2018 should be extrapolated for the scoring algorithm for risk if no acupuncture use, what is the risk for developing/ verse versa for ischemic heart disease.</p> <p>2) I enjoyed reading this paper because this is the only nationwide study that could inform the reality of benefits of acupuncture in co-morbidities issue in a large cohort study. The application of the results should be more in-depth discussed for the protection of the health of Chinese population.</p>

## VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Q1. It is mentioned that the first acupuncture intervention is average 1065 days after the rheumatoid arthritis (RA) - that is a rather long time. About 3 years?

Response:

We appreciate the reviewer's comments. Those are the results from our analyses from the real world database.

Q2. Was there a subset of data where the acupuncture intervention was much earlier, for example in the first 3 months-6 months before chronicity set in?

Response:

We appreciate the Reviewer's comments. We did not set the follow-up period based on acute or chronic stage. The immortal time is the result from the patients meet our inclusion and exclusion criteria. Your comments are the common setting in the clinical trial. But in the real world practice, patients may not do as we expect. In other words, there may not adequate patient could be collected in short follow-up period. Thus, we designed the follow-up period by years.

Q3. This would have been interesting- as if the outcomes were even better, it may mean public health policy may change to include acupuncture in the protocol for RA management. Especially if it reduces the health dollar costs to the individual and the community.

Response:

We appreciate the Reviewer's comments. Although we have positive association between acupuncture use and the lower rate of developing ischemic stroke in the RA patients, the causality could not be obtained from our study design which has been added in the section of limitation in the "Discussion".

Q4. Electroacupuncture (EA) has sometimes been considered better than manual acupuncture- particularly in pain conditions. Comments please. Also why was there only such a small percentage of EA in the sample.

Response:

We appreciate the Reviewer's comments. Your idea is inspiring. And after searching published studies, the results of difference of pain controlling between electroacupuncture and manual acupuncture were variable. There is no definite conclusion. Our result revealed the real world situation about the use of different types of acupuncture intervention in the RA patients. Pain monitoring is not belonged to our outcome measure. These parts would be added the section of in the "Discussion".

Q5. It was stated the standard acupuncture points were used mostly. It would be good to state them eg LI11, ST36, SP9 - whatever selected, as well as having a pictorial / image with the most commonly used points for the readers who are not familiar with acupuncture and its acupoint locations on the body.

Response:

We appreciate the Reviewer's comments. The statements and pictures have been added. Please refer to Lines 2 on Page 16 and Supplementary Fig. 1.

Q6. Please comment about the 10 sessions which was the most common number required for positive change. Is this a biological turning point for acupuncture interventions?

Response:

We appreciate the Reviewer's comments. The treatment dose of acupuncture is an interesting topic. However, there is still no definite conclusion until now. We did not highlight the treatment dose in here because it needs more evidence to confirm its establishment.

Q7. Were the sessions weekly or 2 x a week or a gradual change in frequency. Would increased frequency say from weekly to 2 x a week help in fast tracking reducing the inflammatory state. Please comment.

Response:

We appreciate the Reviewer's comments. The frequency of acupuncture intervention is an important topic in the clinical trial. However, we did not define the criteria of frequency of acupuncture in included patients because the data from real word medical visits. Thus, patient may not follow up suggestion of treatment frequency from medical providers. We would conclude Q6 and Q7 as study limitation in the part of "Discussion".

Q8. Minor English spelling errors for example:

Page 8 Line14 stroke - the spelling

Page 9 Line3 and line 5- stroke- the spelling.

Please check thoroughly.

Response:

We appreciate the Reviewer's comments. These parts have been corrected and we also checked this problem in the whole article.

Reviewer 2

Q1.

In a national wide proposal, this study aims at exploring the benefits of acupuncture for decreasing ischemic stroke in rheumatoid arthritis patients. In pragmatic reality, multi-morbidity has been increasing complicated and it is essential to have public health information to inform public policy for chronic disease management. In a cultural perspective, WHO had published the Traditional Medicine Strategy from 2002 to 2025 and therefore, acupuncture on this issue had become a very important topic to the health of Chinese.

Abstract: As the major finding of the study had identified the number of acupuncture and duration for prevention of Ischemic stroke in this subset of RA patients. The outcomes should explicitly show this results.

Response:

We appreciate the Reviewer's comments.

Q2.

Background:

1) There is a similar study that had published in 2018 in a national wide cohort, what is the difference between this publication with the previous one with coronary heart disease or ischemic stroke. 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.

Response:

We appreciate the Reviewer's comments. Cardiovascular complications are the important issues in the RA patients which included coronary heart disease and ischemic stroke. We have noted the relationships between stroke and RA from meta-analysis (Ref9: Meune, C., Touzé, E., Trinquart, L., & Allanore, Y. (2010). High risk of clinical cardiovascular events in rheumatoid arthritis: levels of

associations of myocardial infarction and stroke through a systematic review and meta-analysis. Archives of cardiovascular diseases, 103(4), 253-261.) and Western agent could lower the risk of stroke (Ref 18. Dhillon N, Liang K. Prevention of stroke in rheumatoid arthritis. Curr Treat Options Neurol 2015;17:356; Ref19. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591-2602.). These inspire us to investigate the effect of stroke prevention from acupuncture which also be found its advantage to control symptoms from RA. From the studies you mentioned and the results from our studies could offer the information about the positive relationship between acupuncture and lowering vascular events in heart and brain, respectively

Q3.

What is the TCM types (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 stands for?

Response:

We appreciate the Reviewer's comments. In Taiwan, patients and medical givers could use manual acupuncture and electroacupuncture in clinical care. We offer the codes to represent these two interventions from our database. Considering your concerns, we deleted the "TCM types" from the original edition. Please refer to Line8 on Page 11.

Q4.

Patients group, intervention, control and outcomes were clearly defined in this cross-sectional study

Response:

We appreciate the Reviewer's comments.

Q5.

Why propensity score of 1:1 were used, please justify this?

Response:

We appreciate the Reviewer's comments. Because the included data came from the real world medical behaviors and the propensity score matching could lower the difference between acupuncture and no-acupuncture cohorts. We used 1:1 matching due to it has lowest bias compared to other ratios (Rassen, J. A., Shelat, A. A., Myers, J., Glynn, R. J., Rothman, K. J., & Schneeweiss, S. (2012). One-to-many propensity score matching in cohort studies. Pharmacoepidemiology and drug safety, 21, 69-80.). And the reference is added as Ref. 54.

Q6. Results

1) 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. This should be highlighted in the abstract.

Response:

We appreciate the Reviewer's comments. The statements have been added in the abstract.

Q7. 1) The application of this results with the year 2018 should be extrapolated for the scoring algorithm for risk if no acupuncture use, what is the risk for developing/ verse versa for ischemic heart disease.

Response:

We appreciate the Reviewer's comments. We followed your suggestions to review the Framingham Risk Score which could calculate the cardiovascular events through personal health status, such as

age, blood pressure, lipid and fasting glucose level, and smoking habit. However, the database we used could not offer the level of blood pressure or lipid concentration. Furthermore, these variables have high correlation with cardiovascular events. And there was no therapeutic intervention included. Thus, acupuncture could be developed into part of algorithm of risk evaluation need more evidence. There was no study reveal their cardiovascular risk algorithm included acupuncture. The idea we add in the limitation of discussion. Please refer to Lines 20-22 on Page 15.

Q8. 2) I enjoyed reading this paper because this is the only nationwide study that could inform the reality of benefits of acupuncture in co-morbidities issue in a large cohort study. The application of the results should be more in-depth discussed for the protection of the health of Chinese population.

Response:

We appreciate the Reviewer's comments.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Quah-Smith, I University of New South Wales
<b>REVIEW RETURNED</b>	01-Oct-2023

<b>GENERAL COMMENTS</b>	In the revision the aims , objectives and discussion are clearer. The conclusion is lack lustre and perhaps ought to include terms such as : acupuncture by reducing pro-inflammatory cytokines, attenuates cardiovascular disease and hence ischaemic stroke. State the outcomes clearly.
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<b>REVIEWER</b>	Wong, Wendy Chinese University of Hong Kong Chung Chi College, The Chinese University of Hong Kong
<b>REVIEW RETURNED</b>	12-Oct-2023

<b>GENERAL COMMENTS</b>	As the PI did respond to every single comment raised. I have no further comment.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Q1. In the revision the aims , objectives and discussion are clearer.

Response:

We appreciate the reviewer's comments.

Q2. The conclusion is lack lustre and perhaps ought to include terms such as : acupuncture by reducing pro-inflammatory cytokines, attenuates cardiovascular disease and hence ischaemic stroke. State the outcomes clearly.

Response:

We appreciate the Reviewer's comments. This part has been added.

Reviewer 2

Q1.

As the PI did respond to every single comment raised. I have no further comment.

Response:

We appreciate the Reviewer's comments.