PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study
AUTHORS	Tsai, Tzung-Yi; Lu, Ming-Chi; Livneh, Hanoch; Chiu, Shan-Yan; Lai, Ning-Sheng; Guo, How-Ran

VERSION 1 - REVIEW

REVIEWER	Karel Kostev IMS Health, Germany; University clinic of Marburg, Germany; Fresenius University, Germany.
REVIEW RETURNED	20-Sep-2016

GENERAL COMMENTS	This is an interesting, well written and clinical important study determined the impact of depression on the stroke risk in RA patients. The authors found out the significant association between RA and the subsequent risk of stroke, but also between depression and stroke in RA patients. The study has several limitations, which were described in the discussion. I see only one problem in study design. Depression diagnosis was defined as diagnosis made between the index date (RA diagnosis or matched index date and stroke). From epidemiological point of view, there is known that each event found between the index date and outcome date is always positively associated with the outcome. If authors would take any other diagnosis or any other prescription given between index date and outcome date, the risk is too high that this diagnosis or prescription will be associated with the outcome. Each diagnosis or prescription increase the observation duration, and longer observation duration is associated with higher risk for outcome. Usually, only baseline variables should be included in regression models. I would ask the authors to perform the sensitivity analyses using any other diagnosis usually not associated with a higher risk of stroke (for example, asthma). Please create the group RA + 'this diagnosis' using the same method as for 'RA + depression'. Then test if this diagnosis has a significant impact on stroke. If it has, then the whole methodology must be changed; then no, please describe it shortly as sensitivity analysis in methods.

REVIEWER	Michael T. Nurmohamed Amsterdam Rheumatology immunology Center | VU University Medical Center & Reade The Netherlands
REVIEW RETURNED	04-Oct-2016

GENERAL COMMENTS	This is an intriguing manuscript that suggests that the risk of stroke in rheumatoid arthritis is enhanced by depression. However, some points deserve attention. Comments - An important drawback is that disease severity markers were not available. Therefore, it can not be excluded that inflammation per se increases the risk of stroke as well as the risk of depression ("the chicken and egg"). Please discuss this point in the discussion section as well as incorporate this aspect into the abstract - p 5- p 8, line 19: please indicate the number of patients - p 6, line 14: please describe the underlying (potential) mechanisms - p 8, line 9/10: how were the strokes verified? - p11, line 43-45: please note that it could also be the other way around (see e.g. D'Mello C, Swain MG. Immune-to-Brain Communication Pathways in Inflammation-Associated Sickness and Depression. Curr Top Behav Neurosci. 2016) - p 13 line 50 - 54: what were the results of this verification process? - p 14, line 55-56: I agree that we should screen our patients for depressive symptoms. However, we also need to know if and to what extent there is a relation with (cumulative) disease activity

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Q1: I would ask the authors to perform the sensitivity analyses using any other diagnosis usually not associated with a higher risk of stroke (for example, asthma). Please create the group RA + 'this diagnosis' using the same method as for 'RA + depression'. Then test if this diagnosis has a significant impact on stroke. If it has, then the whole methodology must be changed; then no, please describe it shortly as sensitivity analysis in methods.
Response: As suggested by the Reviewer, we performed a sensitivity analysis that aimed to examine the stroke risk across three groups, including the reference group, the RA only group, as well as the "RA + asthma" group. The reanalysis showed the "RA + asthma" group had an adjusted HR of 1.18 with a 95% CI of 0.89-1.34, which is not statistically significant. In response to this finding, we added a brief discussion to address the sensitivity analysis done as part of the statistical analysis, which examined the robustness of our study findings. Please refer to lines 15-17 on Page 9 and lines 20-23 on Page 10.

Reviewer 2
Q1: An important drawback is that disease severity markers were not available. Therefore, it can not be excluded that inflammation per se increases the risk of stroke as well as the risk of depression ("the chicken and egg"). Please discuss this point in the discussion section as well as incorporate this aspect into the abstract

Response: We understand the Reviewer's concern and addressed this point in the revised manuscript. Since information on the inflammatory indices was unavailable from this database, we adjusted for this deficit by using the comorbidity variable as a proxy in the multivariate analysis, which may be reflective of the level of inflammation in the body to some extent. This point has been described in the Limitation section. In addition, to further account for the severity level of RA, we also adjusted for the use of medication that was based on whether subjects received DMARDs or biological agents for more than six months after the index date [1, 2]. We noted that 26.9 % (2171/8045) of RA cases received biological agents or DMARDs, while only less than 1% (43/32600) of non-RA patients were prescribed these medications. The reanalysis, taking into consideration the effects of medication usage, indicated that stroke risk for those with RA only and for those with RA and depression, as compared to the general population, was somewhat attenuated but still statistically significant, with the adjusted HRs of 1.23 (95% CI: 1.14-1.32) and 1.98 (95% CI: 1.64-2.22), respectively.

Q2: - p 5- p 8, line 19: please indicate the number of patients
Response: Case numbers of the reference group, those with depression, those with RA, and those RA cases with the depression were: 29,925, 2,675, 6,909, and 1,136, respectively. The exact numbers of these four groups were noted in Table 2 (page 22).

Q3: p 6, line 14: please describe the underlying (potential) mechanisms
Response: There is growing evidence illustrating that the peripheral proinflammatory cytokines may exert potent effects on the pathophysiology of cardiovascular diseases in addition to the effect of unhealthy behaviors and life styles. [3-6] We briefly delineated this point. Please refer to lines 5-17 on page 6.

Q4: p 8, line 9/10: how were the strokes verified?
Response: Stroke incident was defined in accordance with criteria that included at least 3 outpatient service claims, or at least 1 inpatient hospitalization claim since 1996, when the computerized claims from the LHID became available, until the date of cohort entry. This approach has been applied widely to studies using the database. [7-9] Despite the fact that the administrative claims database is affected by the degree of accuracy of diagnosis coding, the approach to coding and the availability of data were similar regardless of RA and depression status in this work. In this respect, we believe that any misclassification bias was likely to be random, and thus would tend to draw the risks estimates to the direction of the null value. Furthermore, the National Health Insurance Bureau of Taiwan often randomly reviews the charts and audits all medical charges, and imposes heavy penalties for any outlier or unsupported charges or malpractice, thus ensuring high quality of useable data. These points were noted in lines 4-6 on page 8, as well as in the Discussion of the revised manuscript (Lines 6-14 on page 14).

Q5: p11, line 43-45: please note that it could also be the other way around (see e.g. D'Mello C, Swain MG. Immune-to-Brain Communication Pathways in Inflammation-Associated Sickness and Depression. Curr Top Behav Neurosci. 2016)
Response: We fully agree that not only the immune-cell-to-brain pathways, but also the gut-microbiota-to-brain routes are involved in the linkage between negative moods and neurological diseases. We added a brief discussion on this issue to the revised manuscript. Please refer to lines 7-11 on page 12.

Q6: - p 13 line 50 - 54: what were the results of this verification process?
Response: In case of any coding errors, the corresponding medical services that clients gave are deducted by the Taiwanese Bureau of NHI (BNHI) and providers are given severe penalties for false diagnosis. We collected data regarding the yearly deducted rate, between 2004 and 2015, from the website of BNHI, and these data showed that the annual deducted rates were less than 1% (Fig. 1),

[10] indicating that the quality of diagnostic codes of the LHID were indeed valid in almost all the cases.

Figure 1. The yearly deducted rate of healthcare services in Taiwan from 2004 to 2015.

Q7: - p 14, line 55-56: I agree that we should screen our patients for depressive symptoms. However, we also need to know if and to what extent there is a relation with (cumulative) disease activity
Response: As suggested by the reviewer, we rewrote these sentences to more accurately describe this concern. Please refer to lines 15-17 on page 15.

REFERENCES

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8. Lu MC, Guo HR, Lin MC, Livneh H, Lai NS, Tsai TY: Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. Scientific Reports 2016, 6:20647.
9. Tsai TY, Livneh H, Lu MC, Tsai PY, Chen PC, Sung FC: Increased risk and related factors of depression among patients with COPD: a population-based cohort study. BMC Public Health 2013, 13(1):976.
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VERSION 2 – REVIEW

REVIEWER	Karel Kostev IMS Health
REVIEW RETURNED	03-Nov-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Michael Nurmohamed Amsterdam Rheumatology immunology Center| VU University Medical Center & Reade

	The Netherlands
REVIEW RETURNED	18-Nov-2016

GENERAL COMMENTS	My comments have been addressed adequately.