PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The risk of dementia in gout and hyperuricemia: A meta-analysis of cohort studies
AUTHORS	pan, shu-yue; Cheng, Rui-Juan; Xia, Zi-jing; Zhang, Qiu-Ping; Liu, Yi

VERSION 1 – REVIEW

REVIEWER	Prof Gavin Reynolds Sheffield Hallam University UK
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	This metanalysis contributes some useful information regarding the relationship of circulating uric acid (UA), in this case in subjects with the high levels associated with gout, to risk of developing a dementing illness. There is already a substantial body of evidence relating UA and dementias, although some is conflicting. A brief check through the introduction identifies multiple errors of which a few are: p7 line 14 “While” is misused. line56 methodological? p8 line 12-14 This is an inaccurate definition of dementia - AD is not normally considered a cerebrovascular disease. line 43 Do they mean “...cognitive function IN such as Parkinson’s...” Reference 4 is inappropriate here since it does not refer either to cognitive deficits or neurodegenerative disorders. I feel some more care was needed in both stating background evidence and providing appropriate citations. There are multiple further examples of poor or incorrect language use throughout the manuscript; for example, plural forms for research and evidence are not usually used. However the meaning is almost always clear. Whether UA is an antioxidant or pro-oxidant is discussed, but with the implication that these are equally valid explanations. UA is well-established as an important circulating antioxidant and free-radical scavenger. Like other antioxidants, ascorbic acid included, it can have some pro-oxidant effects in its oxidised state, but there is relatively very little evidence that this is an important mechanism for circulating UA in comparison to its antioxidant role, notwithstanding some convincing counter-arguments (Sautin and Johnson, 2008). There is also some implicit confusion between its physical deposits stimulating inflammatory response in gout, and its potential contribution as a circulating inflammatory molecule in e.g. atherosclerosis. This needs to be discussed less superficially, if at all. However a more focused approach on UA and dementia in the

	discussion might be an improvement, rather than discussing the presumed inflammatory effects related to a possible elevation in dementia associated with autoimmune diseases. Gout is a very different disorder! While the statistical approach to the metanalysis appears to have been carried out appropriately, with a clear report of the findings, there remains much that is not clear. The sample sizes in each of the four studies would have been valuable to know, as well as in the AD subgroup. More information on the samples would have been useful. For example, dementia is a symptom rather than a disease, while AD is a diagnosed disease partly based on that symptom. What other diseases contributed to the studies? Could the authors have identified whether or not there is an increased risk of vascular dementia, for example? Did the diagnostic criteria for dementia differ between studies? What were they? It would have been valuable to investigate, report or speculate on the reasons for heterogeneity in more detail, rather than just giving us in the somewhat dismissive last sentence of the results.

REVIEWER	Latourte Hôpital Lariboisière, Paris, France
REVIEW RETURNED	28-Jul-2020

GENERAL COMMENTS	In this study, Pan et al. performed a meta-analysis of existing prospective studies to examine the association between hyperuricemia / gout and dementia. Indeed, uric acid being considered a major antioxidant, there is a rationale suggesting that people with hyperuricemia or gout may have a decreased risk for neurodegenerative disorders as compared to healthy controls. Results from existing epidemiological studies are conflicting, and meta-analyses are thus relevant in this context. However, there are several drawbacks to the present study that need to be addressed. My main comments are below. -Some key references in the field that seem to fulfill the inclusion criteria are not included in the present meta-analysis (Euser et al., Brain. 2009 Feb;132(Pt 2):377-82 or Scheepers et al., Alzheimers Dement. 2019 Jun;15(6):754-763). Could the authors explain why those important studies were excluded from the selection? -I strongly recommend against merging studies investigating hyperuricemia and gout. Those two conditions are closely associated, but gout phenotype harbors a lot of confounding factors including higher urate burden, chronic inflammation and the use of anti-inflammatory drugs, the specific effect of urate-lowering therapies, etc etc. Those factors cannot be appropriately addressed by current epidemiological studies, I therefore suggest that hyperuricemia and gout should be examined separately. -Abstract: “Gout is a systemic disease based on abnormal uric acid metabolism”. This statement is somewhat vague. Also in the abstract conclusion, “gout and hyperuricemia have a protective effect on AD”: given the small number of studies included here I think this statement should be tempered. -Strength and limitations section: I don’t understand the following sentence “Our study provides a simple indicator of prognosis management for patients with dementia as a clinical guide”.

	-The methodology for quality assessment of include studies should be detailed more extensively. A ref should be provided for the Newcastle-Ottawa scale. Also, what is meant by “Quality grading: 6-8 stars” in Table 1? -In table 1, I think the column headers do not match the data. Please check the accuracy of the data provided. -The present manuscript contains a lot of typos.

REVIEWER	Haewon Byeon Dept. of Medical Big Data, College of AI Convergence, Inje University, Republic of Korea
REVIEW RETURNED	10-Oct-2020

GENERAL COMMENTS	Thanks for recommending me as a reviewer. This meta-study was conducted to investigate the association between dementia and gout or hyperuricemia. If the authors complete some minor revisions, the quality of the study will be even higher. 1. "Figure 1. Flow diagram" must be rewritten according to the format of PRISMA. 2. In Figure 1, it is necessary to indicate the specific number (n) of each exclusion criterion. For example, authors must present each studies (ex. 31 Case control studies, 5 meta analysis) on the reason why 71 papers were excluded. 3. Line 30-43: The author has a good description of the items(value) used for meta-analysis. Compared to other prior meta-studies, this is great. 4. Page 10, 56- page 11, 30: In this study, the inclusion and exclusion criteria of the manuscript should be described more specifically.

VERSION 1 – AUTHOR RESPONSE

Reply to the comments of Reviewer 1-Gavin Reynolds:
1.p7 line 14 “While” is misused. line56 methodological? p8 line 12-14 This is an inaccurate definition of dementia; AD is not normally considered a cerebrovascular disease. line 43 Do they mean “...cognitive function IN such as Parkinson’s...” Reference 4 is inappropriate here since it does not refer either to cognitive deficits or neurodegenerative disorders. I feel some more care was needed in both stating background evidence and providing appropriate citations. There are multiple further examples of poor or incorrect language use throughout the manuscript; for example, plural forms for research and evidence are not usually used. However, the meaning is almost always clear.
Reply: Thank you for your valuable suggestions. We have modified the incorrect statement, replaced the inappropriate references, and enlisted a professional editing service to help us polish the manuscript.

2. Whether UA is an antioxidant or pro-oxidant is discussed, but with the implication that these are equally valid explanations. UA is well-established as an important circulating antioxidant and free-radical scavenger. Like other antioxidants, ascorbic acid included, it can have some pro-oxidant effects in its oxidised state, but there is relatively very little evidence that this is an important

mechanism for circulating UA in comparison to its antioxidant role, notwithstanding some convincing counter-arguments (Sautin and Johnson, 2008). There is also some implicit confusion between its physical deposits stimulating inflammatory response in gout, and its potential contribution as a circulating inflammatory molecule in e.g. atherosclerosis. This needs to be discussed less superficially, if at all. However a more focused approach on UA and dementia in the discussion might be an improvement, rather than discussing the presumed inflammatory effects related to a possible elevation in dementia associated with autoimmune diseases. Gout is a very different disorder!
Reply: Thank you for your valuable advice. We have revised the content of our discussion.
3. While the statistical approach to the meta analysis appears to have been carried out appropriately, with a clear report of the findings, there remains much that is not clear. The sample sizes in each of the four studies would have been valuable to know, as well as in the AD subgroup. More information on the samples would have been useful. For example, dementia is a symptom rather than a disease, while AD is a diagnosed disease partly based on that symptom. What other diseases contributed to the studies? Could the authors have identified whether or not there is an increased risk of vascular dementia, for example? Did the diagnostic criteria for dementia differ between studies? What were they? It would have been valuable to investigate, report or speculate on the reasons for heterogeneity in more detail, rather than just giving us in the somewhat dismissive last sentence of the results.
Reply: We list the detailed data of sample sizes in Table 1, including the AD subgroup. Among the four articles included in our meta-analysis, only one article described that patients with gout had a lower risk of developing vascular dementia (VD). The diagnostic criteria for dementia may differ between studies. Lu et al. used AD diagnostic codes that were shown to have a positive predictive value of 83% in a validation study based on the UK GPRD as diagnostic criteria. In Singh et al. and Hong et al.'s articles, the ICD9-CM was used to provide diagnostic criteria for dementia. In Latourte et al.'s article, they used DSM-IV as diagnostic criteria for dementia, and used NINCDS-ADRDA as diagnostic criteria for AD. In our results, we tried our best to report or specify the reasons for heterogeneity in more detail.
Although studies differed by publication of year, race, sample size, and mean age, meta-analysis did not find any association with these factors. The reasons for high heterogeneity are considered to be related to differences in countries, environmental factors, clinical features, and a lack of uniform designs, uniform inclusion criteria, and uniform follow-up durations, which may affect the generalizability of the final result.

Reply to Reviewer 2-Augustin Latourte's comments:
1.Some key references in the field that seem to fulfill the inclusion criteria are not included in the present meta-analysis (Euser et al., Brain. 2009 Feb;132(Pt 2):377-82 or Scheepers et al., Alzheimers Dement. 2019 Jun;15(6):754-763). Could the authors explain why those important studies were excluded from the selection?
Reply: Thank you for your comments. The two articles mentioned by Professor Augustin Latourte are valuable articles, and we have read them carefully before we sort out the data for this meta-analysis. However, the data of these two articles do not meet our inclusion criteria, and the relevant data cannot be extracted. Therefore, those studies were excluded from the selection.

2. I strongly recommend against merging studies investigating hyperuricemia and gout. Those two conditions are closely associated, but gout phenotype harbors a lot of confounding factors including higher urate burden, chronic inflammation and the use of anti-inflammatory drugs, the specific effect of urate-lowering therapies, etc etc. Those factors cannot be appropriately addressed by current epidemiological studies, I therefore suggest that hyperuricemia and gout should be examined separately.
Reply: As professor Augustin Latourte said, Indeed, hyperuricemia and gout are closely associated. Hyperuricemia is an indispensable factor in the pathogenesis of gout. Moreover, the number of related research articles is limited, and more relevant data cannot be collected. Based on the above considerations, gout and hyperuricemia were still analyzed in this meta-analysis. We will continue to

pay close attention to the relevant literature of this type of research in future, collect more data for future research, and make our research more specific and detailed. Thank you for your valuable advice.

3. Abstract: “Gout is a systemic disease based on abnormal uric acid metabolism”. This statement is somewhat vague. Also in the abstract conclusion, “gout and hyperuricemia have a protective effect on AD”: given the small number of studies included here I think this statement should be tempered.
Reply: Thank you for your advice. We have revised this in the abstract of our manuscript.

4. Strength and limitations section: I don’t understand the following sentence “Our study provides a simple indicator of prognosis management for patients with dementia as a clinical guide”.
Reply: Thank you for your comments. We have revised the Strength and Limitations section in our manuscript.

5. The methodology for quality assessment of include studies should be detailed more extensively. A ref should be provided for the Newcastle-Ottawa scale. Also, what is meant by “Quality grading: 6-8 stars” in Table 1?
Reply: We have provided the Newcastle–Ottawa scale as a supplementary material. We used the Newcastle–Ottawa scale to assess the quality of individual studies. In short, a maximum of 9 points was assigned to each study: 4 for selection, 2 for comparability, and 3 for outcomes. A final score >5 points was regarded as high quality. We have revised this in Table 1. Thank you for your advice.

6. In table 1, I think the column headers do not match the data. Please check the accuracy of the data provided.
Reply: Thank you for your comments. We have carefully revised and checked Table 1 in our manuscript.

7. The present manuscript contains a lot of typos.
Reply: We have carefully revised our manuscript again and polished our revised manuscript with the help of a professional editing service.

Reply to Reviewer 3-Haewon Byeon’s comments:
1. "Figure 1. Flow diagram" must be rewritten according to the format of PRISMA.
2. In Figure 1, it is necessary to indicate the specific number (n) of each exclusion criterion. For example, authors must present each studies (ex. 31 Case control studies, 5 meta analysis) on the reason why 71 papers were excluded.
Reply: We have revised “Figure 1.Flow diagram” in the images file, according to the format of PRISMA.

3. Line 30-43: The author has a good description of the items (value) used for meta-analysis. Compared to other prior meta-studies, this is great.
Reply: Thank you for your affirmation of our work.

4. Page 10, 56- page 11, 30: In this study, the inclusion and exclusion criteria of the manuscript should be described more specifically.
Reply: Thank you for your comment. We have described the inclusion and exclusion criteria of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Prof Gavin Reynolds Sheffield Hallam University Sheffield UK
REVIEW RETURNED	29-Nov-2020

GENERAL COMMENTS	The authors have addressed the points I raised adequately. There remain a few idiosyncrasies of language. It is reassuring that results from our own small study showing an association of reduced uric acid with AD but not vascular dementia are consistent with this large meta-analysis!

REVIEWER	Augustin Latourte Rheumatlogy department and Inserm 1132, Lariboisiere Hospital, AP-HP, Université de Paris, Paris, France
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	The authors did a nice work and the manuscript has greatly improved upon revision. I only have a few comments to discuss with the authors : 1- My main concern is still that hyperuricemia (HU) and gout are two closely associated yet very different conditions. A majority of people with asymptomatic HU will never have gout, and gout affects likely those with the highest urate burden. Moreover, unlike those with asymptomatic HU, patients with gout receive anti-inflammatory or urate-lowering therapies and one cannot exclude that those drugs impact the risk of dementia. I understand that the authors have decided to merge studies invesigating HU and gout to increase the sample size, but I suggest that since 3 out of the 4 studies included investigated gout, a supplementary analysis focusing on gout should be conducted. This should also be discussed properly in the discussion. 2- Moreover, I understand why the authors excluded the studies published by Euser (Brain 2009) and Scheepers (Alzheimers Dementia 2019) from the meta-analysis. Yet, they are of major interest in the field and their results should at least be discussed in the discussion section. I have some additional minor comments : p.9 « only one described a lower risk of developing vascular dementia (VD) in patients with gout » : please provide the reference. p.9 « Hyperuricemia causes persistent low-grade systemic inflammation of gout » : do the authors mean « AND gout » ? p.10 « Mollenhauer et al. compared 135 new-onset PD patients » : PD likely results from completely different processes and may not be comparable to other causes of dementia like AD. I suggest that the authors drop this sentence.

VERSION 2 – AUTHOR RESPONSE

Reply to Reviewer2- Dr. Augustin Latourte's comments:

1- My main concern is still that hyperuricemia (HU) and gout are two closely associated yet very different conditions. A majority of people with asymptomatic HU will never have gout, and gout affects likely those with the highest urate burden. Moreover, unlike those with asymptomatic HU, patients with gout receive anti-inflammatory or urate-lowering therapies and one cannot exclude that those drugs impact the risk of dementia. I understand that the authors have decided to merge studies invesigating HU and gout to increase the sample size, but I suggest that since 3 out of the 4 studies included investigated gout, a supplementary analysis focusing on gout should be conducted. This should also be discussed properly in the discussion.

Reply: Thank you for your advice. In our discussion section, we further explored the relationship between gout and dementia. We hope that our research will arouse more interest among doctors and researchers on the relationship between uric acid level and dementia.

2- Moreover, I understand why the authors excluded the studies published by Euser (Brain 2009) and Scheepers (Alzheimers Dementia 2019) from the meta-analysis. Yet, they are of major interest in the field and their results should at least be discussed in the discussion section.

Reply: thanks for your valuable advice. Their results were discussed in our discussion section.

3- p.9 « only one described a lower risk of developing vascular dementia (VD) in patients with gout » : please provide the reference.

Reply: thank you for your comments. We have provided the reference in our manuscript.

4-p.9 « Hyperuricemia causes persistent low-grade systemic inflammation of gout » : do the authors mean « AND gout » ?

Reply: thanks for your valuable advice. We have revised this sentence in our manuscript.

5-p.10 « Mollenhauer et al. compared 135 new-onset PD patients » : PD likely results from completely different processes and may not be comparable to other causes of dementia like AD. I suggest that the authors drop this sentence.

Reply: thanks for your suggestion. We have dropped this sentence.

VERSION 3 – REVIEW

REVIEWER	Augustin Latourte Université de Paris, APHP, France
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	The authors have addressed my comments appropriately. The manuscript (especially the discussion section) is improved. I have no further comments.