Author’s response to reviews

Title: Gout is associated with a higher risk of Chronic Renal Disease in Older Adults: A Retrospective Cohort study of U.S. Medicare population

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Author’s response to reviews:

We thank the reviewers for their helpful comments, which have helped us improve the quality of our paper. Following are our point-by-point responses to the comments.

Editor Comments:

In addition to the referee comments, please address the following editorial points:

As a discretionary change, please add more detail/context for your study to the abstract background (e.g. the population you studied, why the study is needed etc.). Please ensure any changes to the abstract are also updated in the version in the online submission system.

Response: We have expanded the background section in the abstract as recommended.

“Background: Hyperuricemia and gout have been linked to chronic kidney disease (CKD). Whether the increased risk of CKD in gout is due to shared risk factors such as hypertension, diabetes or heart disease, or due to gout itself is not known. Studies in older adults, who tend to have a high incidence of CKD, are limited. Our objective was to assess whether gout was associated with incident CKD in older adults.”
Please also ensure all section headings are as outlined in the submission guidelines, including the addition of a conclusion section.

Response: We have added a conclusion title and done as suggested.

Reviewer reports:

Timothy Jansen (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Interesting analysis of a significant population

Response: Thank you.

Major issue:

1- calculate HR or Odds in patients using less potent XOI doses vs potent XOI doses as surrogate to show that lower uric acid levels may be beneficial regarding CKD evolution

2- regarding recent issue on febuxostat vs allopurinol: did the authors find significant differences between these subgroups?
Response: We appreciate the two comments. The requested analyses have been previously published in a separate paper that focused on comparative effectiveness of febuxostat and allopurinol and ULT doses for renal function preservation. This previous study found differences between allopurinol and febuxostat and an association with ULT dose with incident renal disease. These published analyses might also be somewhat outside the scope of the current paper, which was focused on assessing gout as a risk factor for CKD.

Reviewer 2 (Reviewer 2): PEER REVIEWER COMMENTS: To view the full report from the academic peer reviewer, please see the attached file.

Reviewer 2 (Reviewer 2): PEER REVIEWER COMMENTS: To view the full report from the academic peer reviewer, please see the attached file.

Response: We reviewed the attached file and it has the same comments as listed below.

REVIEWER COMMENTS FROM REPORT: The study is interesting and important.

Strengths include the large representative sample and the inclusion of sensitivity analyses to provide further insights into the findings.

Response: Thank you.

I do have some concerns, however, about the definitions and description of exposure and outcomes and additional confounding variables, which were not adjusted for.
REQUESTED REVISIONS: More information is required about the definition of chronic kidney disease (CKD) and its prior validation. How do ICD-9 codes map to the National Kidney Foundation stage 1-5 classification that is commonly used for research purposes and in clinical practice? In the National Kidney Foundation classification system, only stages 3-5 are considered to be clinically significant, so it is important to know whether CKD in this study, defined using ICD-9 codes, includes milder (stage 2) CKD, as this has significant implications for the clinical significance of the study findings and for comparing to the existing literature.

Response: The ICD-9 code approach has been validated and this information was provided in this section, more details have been added per reviewer request, also pasted below again for reviewer’s convenience. This approach has been used both in the most commonly used comorbidity index, the Charlson index and its various adaptations and by the U.S. Renal Data System Coordinating Center.

The ICD-9 codes for CKD include NKF CKD stages 2-5. We have added this detail to discussion and limitations.

“This approach is valid with high specificity of 99% and moderate sensitivity of 70-88% [10] and a median positive predictive value of 78% [11].”

“This ICD-9-CM code based approach has been used to assess renal disease in the validated Charlson-Romano comorbidity index [7] (commonly used comorbidity index), and is being currently used by the U.S. Renal Data System Coordinating Center [8].”

“This definition of incident CKD has been used in several high-quality studies [39-42] and being currently used by the U.S. Renal Data System Coordinating Center [8].”

“These ICD-9 codes include all CKD stages of the National Kidney Foundation classification of CKD.”
“We realize that this ICD-9-code based approach includes all CKD stages of the National Kidney Foundation classification of CKD. Since milder kidney disease such as the CKD stage 2 likely has different outcomes than CKD stages 3-5, future studies need to investigate the risk of different stages of CKD in larger patient samples.”

Did the confounding medications include angiotension II receptor antagonists, which associate with hyperuricaemia and gout in different ways (losartan being protective, others predisposing)? A further important confounder that is not considered is non-steroidal anti-inflammatory drugs, which are commonly used by people with gout and are an established risk factor for CKD. Confounding medications adjusted for in the analysis (cardiovascular medications, allopurinol, febuxostat) should be added to Table 1.

Response: We list the lack of control for ARBs and NSAIDs as study limitations. Most NSAIDs in the US are used over-the-counter, therefore it can be adequately controlled in a claims database study. The medication use of cardiovascular disease and gout were time-varying covariates. People with and without incident CKD contributed both medication exposed and medication unexposed periods to the analyses, as per the study design. Therefore, presenting simple frequencies of each drug exposure in Table 1 is not feasible and will be inaccurate and misleading.

“However, we were unable to control for other minor risk factors such as smoking, and genetics due to the absence of these data in Medicare data; and the use of non-steroidal anti-inflammatory drugs (NSAIDs) since the majority use in the U.S. is non-prescription, which is not available in the Medicare database. We did not control for the use of angiotension II receptor antagonists, which are nephroprotective.”

I find the description of predictor and outcome of interest on pg 4 (methods) confusing. As I understand the design, people who did and did not have gout (the exposure) were followed to compare the incidence of CKD (the outcome) between the exposed and unexposed groups. Yet on page 4, the predictor is said to be CKD and the outcome gout, which implies the opposite, that people with and without CKD were followed to compare the incidence of gout.
Response: We sincerely thank the reviewer for pointing out this typographical error and regret the inconvenience and confusion this led to. The reviewer is correct, gout is the exposure variable and new CKD is the outcome of interest. We have carefully examined the entire paper. We have corrected this error and did not find any similar errors in the report.

“Independent Variable/Outcome of interest

The outcome of interest was incident chronic kidney disease (CKD), identified by the occurrence of ……

Predictor of interest

Gout was the main exposure of interest, i.e., the independent variable.”

Similar confusion is seen in the first paragraph of the results, which makes a statement comparing the characteristics of people with gout versus those without, signposting Table 1, yet Table 1 compares people with and without incident CKD. Table 1 would be informative if it matched the text and compared those with and without gout at baseline (assuming that my understanding of the design outlined in the preceding point is true).

Response: The reviewer is correct and we agree. We have re-arranged the results as recommended. Table 1 now matches with the text in results paragraph 1. We have added another table comparing the characteristics of people with and without gout is provided in Appendix 1.

“Of the 1,699,613 eligible people, 168,065 developed incident CKD. Compared to people without CKD, people with CKD were 1.5 years older, had one more medical comorbidity and more likely to be male, African-American, and have each of the 17 Charlson-Romano comorbidities, as well as hypertension, hyperlipidemia and coronary artery disease (Table 1). Comparison of characteristics of people with and without gout is provided in Appendix 1.

Incident CKD developed in 150,162 people without gout and 17,903 people with gout, with crude respective incidence rates of 15.6 vs. 78.1 per 1,000 person-years.”
References: