PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018
AUTHORS	Liang, Zhenguo; WU, Dongze; Zhang, Hua; Gu, Jieruo

VERSION 1 – REVIEW

REVIEWER	Clavijo-Cornejo, Denise Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra
REVIEW RETURNED	05-May-2023

GENERAL COMMENTS	The manuscript by Zhenguo Liang et al aims to describe association between asymptomatic hyperuricemia and the risk of arthritis, studding a total of 13,647 eligible participants from the US National Survey 2007- 2018. The main contribution is the suggestion that asymptomatic hyperuricemia is prior to osteoarthritis and the use of a representative sample from the United States. The main limitations are well described by the authors. There are some general comments: > I suggest to describe the characteristics of the healthy control group in the “Study population” section. > It is also important to take into account the sex-specific cut-off point of the uric acid level. The hyperuricemia has been reported as serum uric acid ≥5.3 mg/dL for women and ≥ 6.2 mg/dL for men. > In the results, it is necessary to specify the table number to easily track the results in each paragraph. > The number of subjects excluded in the flow chart (figure 1), do not correspond with the “Study population” section, in particular in the line 118 “…incomplete BMI, uric value, and smoking record (n=6,799)” in the flow chart the mentioned excluded number is 2,549. > In the references there are some recent articles that I suggest to include in the manuscript: T.-N. Cao et al., Association between asymptomatic hyperuricemia and knee osteoarthritis in older outpatients, 2015-2040. Eur Rev Med Pharmacol Sci, 2022 Sep;26(18):6600-6607. Xiaopeng Liang et al., Is hypertension associated with arthritis? The United States national health and nutrition examination survey 1999-2018. Ann Med, 2022 Dec;54(1):1767-1775.

	> In the section of “Contributor”, I suggest to mention the full name of Prof. JRG. > There are some spell mistakes (example: line 70, “comm” instead of “common”; line 144, “and diabetes”; line 145, Race”/”; line 187, there is an extra space at the end of the paragraph; line 197, there is an extra period at the end of the paragraph; in the line 135, “We put” etc.) I suggest to review all the manuscript to find the spell mistakes.

REVIEWER	Pillinger, Michael New York University Grossman School of Medicine, Medicine/Rheumatology
REVIEW RETURNED	11-Sep-2023

GENERAL COMMENTS	

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GENERAL COMMENTS	

VERSION 1 – AUTHOR RESPONSE

This cross-sectional study addresses an important question—whether there could be an association between asymptomatic hyperuricemia and osteoarthritis. The methods section and statistical analysis are well-organized. The subsections and tables are organized in a logical fashion. Using weighted values from NHANES MEC examination weights, this study compared baseline characteristics of arthritis groups vs. non-arthritis group, reinforcing that the prevalence of arthritis is higher in females than males (Table 1). Table 2 then outlines the baseline characteristics comparing the high uric acid group vs the healthy control group. After adjusting for confounders, the association between AH and arthritis was no longer significant in the total population (Table 3). In the subgroup analysis, the relationship between AH and arthritis remained insignificant across all age groups after adjusting for all the confounding risk factors (model 3). Only in non-Hispanic Blacks did asymptomatic hyperuricemia remain significantly associated with arthritis (Model 3, Table 4).

Major comments
o The authors did an excellent job with the data analysis. However, a professional round of language editing would better showcase their results and improve readability of the paper. There are several instances where the message is lost in translation. For example, lines 78-80 is not a complete sentence. Perhaps you were trying to state, “the true importance of AH as a risk factor for incident gout is unknown as only half of patients with longstanding hyperuricemia develop clinically evident gout over 15 years”? Another example is lines 86-88—this sentence may benefit from being separated into two sentences. Perhaps you were trying to say, “Hyperuricemia and OA are driven by

common risk factors such as obesity and aging." However, it is then unclear how this point links to "intraarticular urate result in urate crystallization and deposition on the cartilage, disruption of cartilage by promotes urate crystallization and deposition". Another example is lines 139-144—Consider rewriting the sentence as, "Covariates that could confound the association between OA and AH were selected based on...". Another example is lines 207-208—perhaps you were trying to say, "Those over age 50 years old were more likely to have OA, RA, other/don't know arthritis than no arthritis"?

o In the discussion, the first line can be misleading as it states the data showed a relationship between AH and incident arthritis. Similarly, page 17 line 43 – stating that "Our data confirms that AH is a danger signal of increasing risk for OA" is broad-sweeping and can erroneously imply that increasing levels of hyperuricemia increases the risk for OA-which was not shown in this study. (Also, the term "danger signal" is actually a term of use that refers to the ability of intracellular degradation products to activate innate immune receptors such as toll-like receptors—a better term might be "marker".) My understanding is that in total participants, the relationship between AH and OA did not remain significant after adjusting for confounding risk factors (Table 3). Then again, in the subgroup analysis model 3 where all confounders were adjusted for, the data showed that AH and OA relationship was insignificant across all age groups (Model 3, Table 4).

o In the discussion, first line, you cannot use the term incident arthritis because this is a cross-sectional study. There are other instances of this in the manuscript that should be addressed. For example, Page 16- Line 43? Cannot say "associated with new development of arthritis" – because that's not prevalence. Another example is Page 18- Line 36 –Consider changing to, "…AH are more likely to HAVE OA…" rather than develop OA.
o

o In the discussion, the authors should explore why arthritis was not independently associated with AH after adjusting for confounding risk factors. For example, why was the association between AH and OA insignificant in Model 3 (after additionally adjusting for cholesterol and creatinine)? Do you think cholesterol and creatinine made the difference between Model 2 and 3? In the subgroup analysis (Table 4), why is AH significantly associated with arthritis only in non-Hispanic blacks (page 16, model 3)? Do these results suggest that these subgroups of patients (ie non-Hispanic blacks) are more likely to benefit from urate lowering therapies for treatment of their osteoarthritis? What are the implications of these findings?

o Lines 197-199 – Is the difference found in the 50-59 age group only or with the total group?
o Page 15- Table 3 – P-values are noted to be significant in the table, but the confidence intervals cross 1. Additionally, the title does not match the content of the table. Is this looking at the association between asymptomatic hyperuricemia and total arthritis or is this regarding osteoarthritis only?
o Page 16- Likewise, does Table 4 describe total arthritis or osteoarthritis only?
o Table 4- Consider dividing the Hispanic population into two groups: White and Black Hispanics, like you did for non-Hispanic White and Non-Hispanic Black
o Page 16- Lines 51-55 – Only OA was significant, other arthritis, RA, Don't know, were all not significant thus this can be misleading.

Minor comments
o The labeled Lines of this document stops at Line 218 and is discontinued after Table 1. Makes it difficult to comment line by line.
o Page 17- In discussion, second paragraph, first sentence, needs a reference for "accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic arthritis, and spondylarthritis"
o Line 202- Misspelled osteoarthritis

o Table 1 Line 213- “Don’t know” misspelled
o Consider changing category “don’t know of arthritis” to “unspecified arthritis”
o Lines 67-69 rephrase to “…risk factors that are in most need for intervention”
o Lines 74-76 can be simplified with professional language editing
o Line 83-85 should be rephrased to better connect the two ideas stated
o In the discussion, second and third sentences discussing epidemiology are better suited for the introduction
o Page 17- Discussion, second paragraph, make sure to consistently use acronyms—if using RA, stick with RA instead of writing rheumatoid arthritis
o Page 17- Discussion, third paragraph, first sentence—cannot use the term danger signal because it suggests it is an activator of leukocytes
o Page 17- Discussion, third paragraph – To strengthen your point, consider referencing: Serum Urate Levels Predict Joint Space Narrowing in Non-gout Patients with Medial Knee Osteoarthritis https://pubmed.ncbi.nlm.nih.gov/28217895/
o Page 18- Line 17 – Opioids are not recommended for treatment of OA
o Page 18- Line 29 – Because it is still unknown whether urate lowering decreases risk for OA, perhaps rephrase sentence to, “our results raise the prossibility that pharmacologic treatment of AH…” (rather than suggest)
o Page 18- Line 45 – Change to serum urate rather than uric acid levels
o Page 18- Lines 54- 55 – Consider changing to “Serum Urate levels were significantly associated with knee OA as determined by osteophytosis in men but not in women.”

I note that Dr. Nicole Leung contributed to this review with me.

Michael Pillinger, MD