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Allopurinol use and the risk of dementia

A meta-analysis of case–control studies

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Abstract

Background. This study aimed to compare the risk of dementia between exposed to allopurinol and not exposed to allopurinol in persons who had gout and/or hyperuricemia.

Methods. The meta-analysis was conducted to select case–control research written in English through the help of PubMed and Web of Science. The pooled odds ratio (OR) with 95% confidence interval based on the fixed-effect model was applied to compare the allopurinol exposure among cases (subjects with dementia) and controls (subjects without dementia).

Results. A total of 4 case–control studies relating the allopurinol exposure to the risk of dementia were identified. The study duration was from 9 to 14 years. The number of study persons was from 3148 to 137,640. The male percentage of study subjects was from 36.9 to 62.5. The mean age of study persons was from 72.3 to 78.7 years. Overall, the odds of the allopurinol exposure among cases were lower than the odds of the allopurinol exposure among control subjects (OR = 0.91, 95% confidence interval = 0.87–0.95, $P < .001$). The heterogeneity between these eligible studies was low ($I^2 = 0\%$). The sensitivity analysis revealed that after excluding the studies with concern, the pooled OR did not achieve statistical significance.

Conclusions. This is the first meta-analysis to report that there is a negative relationship between the allopurinol exposure and the risk of dementia. Although the results favor the hypothesis, currently it is unable to draw strong conclusions about the protective effect of allopurinol against dementia due to inclusion of only a few eligible studies. Randomized controlled trials are needed to explore the relationship between allopurinol exposure and the probability of dementia.

Abbreviations: 95% CI = 95% confidence interval, OR = odds ratio.

Keywords: allopurinol, case–control, dementia, gout, hyperuricemia, meta-analysis

1. Introduction

Epidemiological research has approved that high serum uric acid is a key risk for gout and also is recognized as a potential risk for cardiovascular disease.[1] Uric acid in humans has an antioxidant capacity, which is considered to be a protector against neurodegenerative diseases.[2,3] But the results still contain conflicting evidence. Some studies revealed that high serum uric acid correlated with a decrease in the risk of dementia or cognitive dysfunction.[4,5] Others revealed that high serum uric acid correlated with an increase in the probability of dementia.[6,7] The meta-analysis revealed that the relationship between the serum uric acid and the probability of dementia remains to be inconsistent due to high heterogeneity between studies.[8]

Allopurinol is commonly used to manage gout/hyperuricemia based on its uric acid-lowering capacity through inhibiting xanthine oxidase. Based on its uric acid-lowering capacity, epidemiological studies have explored the relationship between the use of allopurinol and the probability of dementia, but the results were not consistent. Some studies showed allopurinol having a protective effect against dementia,[9,10] but others showed no correlation between the use of allopurinol and the probability of dementia.[11–14] In light of these controversial results, we performed a meta-analysis to better understand the relationship between the use of allopurinol

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethical approval was not required because the study was a meta-analysis of published literature.

All data were adapted from published studies.

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Key points

1. What is the main question addressed by this study?
   To compare the risk of dementia among subjects exposed to versus not exposed to allopurinol.
2. What are the main findings of this study?
   The odds of the allopurinol exposure among cases were lower than the odds of the allopurinol exposure among controls.
   After excluding the studies with concern, the pooled odds ratio did not achieve statistical significance.
3. What is the meaning of the finding?
   Currently, it is unable to draw strong conclusions about the protective effect of allopurinol against dementia due to inclusion of only a few eligible studies.

and the probability of dementia in persons with gout and/or hyperuricemia.

2. Methods

2.1. Literature search

We addressed the research concept in a PICO summary: population (P), persons with gout and/or hyperuricemia; intervention (I), the use of allopurinol; comparator (C), nonuse of allopurinol; outcome (O), the new diagnosis of dementia.

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines,[15] we underwent a meta-analysis of the existing literature. We used PubMed and Web of Science to select the related literature published during the time from January 2000 to July 2021. The literature was limited to cohort design and case–control design written in English. The following keywords were used to select the relevant literature: dementia (title) and gout (title), dementia (title) and uric acid (title), dementia (title) and hyperuricemia (title), dementia (title) and allopurinol (title), dementia (title) and urate-lowering (title), dementia (title) and uric acid-lowering (title), Alzheimer's disease (title) and gout (title), Alzheimer's disease (title) and uric acid (title), Alzheimer's disease (title) and hyperuricemia (title), Alzheimer's disease (title) and allopurinol (title), Alzheimer's disease (title) and urate-lowering (title), as well as Alzheimer's disease (title) and uric acid-lowering (title). The deadline for literature search was on July 31, 2021.

2.2. Inclusion criteria

The following inclusion criteria were applied: cohort design including subjects diagnosed with gout and/or hyperuricemia at baseline, comparing people with and without allopurinol use, and finally using dementia or Alzheimer disease as the main outcome; case–control design which included subjects diagnosed with dementia or Alzheimer disease as cases and subjects without any type of dementia as control subjects. The investigators retrospectively compared subjects with the use of allopurinol and nonuse of allopurinol between cases and control subjects.

2.3. Extraction of data

The literature review was done by 2 investigators (K.-F.L. and Y.-H.K.). The following variables were extracted from individual studies: the first author's family name, publication year, database name, study design, study duration, sample size, percentage of males, mean age, adjusted odds ratio (OR) and 95% confidence interval (CI), bias, as well as limitation. The disagreement was resolved through consensus by 2 investigators (B.-F.H. and C.-S.L.).

2.4. Risk of bias assessment

The quality of all eligible studies was examined according to the Newcastle-Ottawa Scale (NOS) system.[16] A NOS score ≥8 is regarded as a high-quality study.

2.5. Statistical analysis

A fixed-effect model was applied to assess the pooled odds ratio (OR) with 95% CI for the relationship between the exposure of allopurinol and the probability of dementia. The I^2 and Q statistics were applied to assess the heterogeneity of included studies,[17] and I^2 of >50% suggested a significant heterogeneity of included studies. The statistical analyses were done by the help of a Cochrane Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). The P value <.05 was set as statistically significant.

3. Results

3.1. Information of included studies

Figure 1 reveals a flowchart of literature search. A total of 4 case–control studies relating the allopurinol exposure to the risk of dementia were identified. All 4 studies were based on the analysis of claims data. The information of 4 case–control studies was revealed in Table 1. Four case–control studies had been published in 2018–2021. The study duration was from 9 to 14 years. The number of study persons was from 3148 to 137,640. The male percentage of study persons was from 36.9 to 62.5. The mean age of study persons was from 72.3 to 78.7 years. Some bias existed in the 4 case–control studies.

One case–control study of Engel et al[10] disclosed a negative relationship between the allopurinol exposure and the probability of dementia, but the other 3 case–control studies disclosed no association.[12–14]

The NOS score was 7 in 4 case–control studies.

3.2. Pooled OR for the association between allopurinol exposure and dementia

The forest plot in Figure 2 reveals a pooled OR with 95% CI for the relationship between the allopurinol exposure and dementia. Overall, the odds of the allopurinol exposure among subjects with dementia showed lower than the odds of the allopurinol exposure among control subjects (OR = 0.91, 95% CI = 0.87–0.95 and P < .001). The heterogeneity between these eligible studies was low (I^2 = 0%).

3.3. Sensitivity analysis and publication bias

Two papers from Engel et al[10] and Min et al[12] only showed the effect of total urate-lowering agents. The study of Engel et al[10] addressed that allopurinol accounted for 98.4% of the total urate-lowering agents, but the individual OR and 95% CI for allopurinol use were not provided. The study of Min et al[12] addressed that there was no significant correlation between the use of allopurinol and the probability of dementia, but the OR and 95% CI were not shown. After excluding these 2 studies of Engel et al and Min et al, a pooled OR was 1.0 (95% CI = 0.87–1.14 and P = .99). It did not achieve statistical significance. The study by Engel et al[10] had largest sample sizes (n = 137,640). After excluding the study by Engel et al, the pooled OR was 0.94 (95% CI = 0.88–1.02 and P = .13). It did not achieve statistical significance.

A visual inspection of a funnel plot disclosed symmetry (see Figure S1, Supplementary Digital Content, http://links.lww.com/MD/G837). The symmetry was confirmed by both Begg test and Egger test (P =.1742 and P = .0589, respectively),[18,19] without

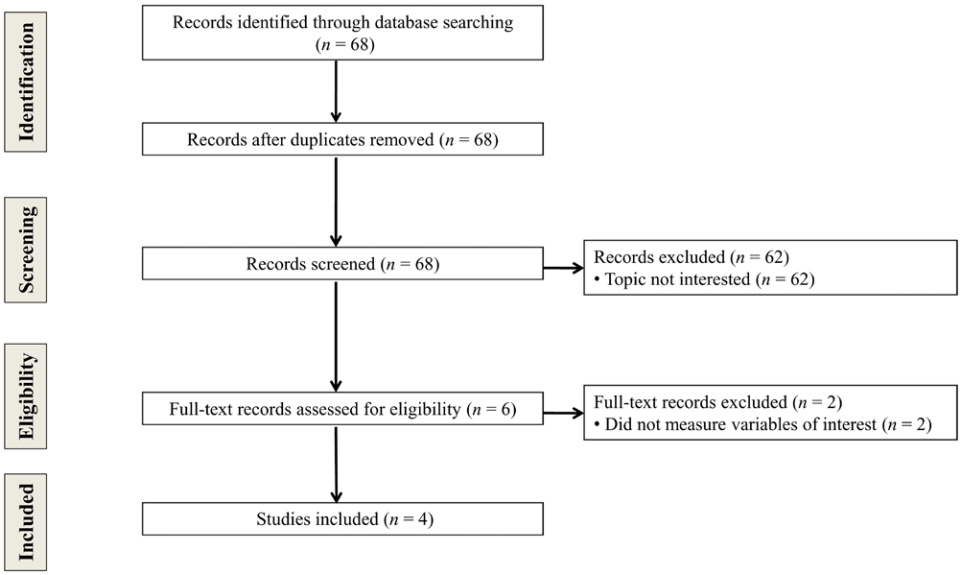

Figure 1. Flowchart of literature search.

Table 1

Characteristics of eligible studies included in a meta-analysis (case–control study).

Author, year	Data source	Study design	Study period	Sample size	Cases of dementia (n)	Controls (n)	Male (%)	Age, yr, mean (SD)	Adjusted OR (95% CI)	Bias	Limitation	Study quality (NOS score)
Engel et al, 2018[10]	AOK	Case–control study	2004–2013	137,640	27,528	110,112	36.9	74.0 (6.5)	0.89 (0.85–0.94)	Misclassification, surveillance, confounding	No serum data, no lifestyle information	7
Min et al, 2021[12]	NHIS database	Nested case–control study	2002–2013	12,784	2557	10,227	62.5	72.3 (6.1)	0.92 (0.84-1.01)	Misclassification, surveillance, confounding	No serum data, no lifestyle information	7
Chuang et al, 2021[13]	Taiwan NHIRD	Nested case–control study	2005–2013	3242	1621	1621	59.8	76.9 (7.1)	1.02 (0.86–1.22)	Misclassification, surveillance, confounding	No serum data, no lifestyle information	7
Lai et al, 2021[14]	Taiwan NHIRD	Case–control study	2000–2013	3148	1574	1574	43.6	78.7 (6.6)	0.97 (0.79–1.20)	Misclassification, surveillance, confounding	No serum data, no lifestyle information	7

AOK = Allgemeine Ortskrankenkasse, German statutory health insurance, 95% CI = 95% confidence interval, NHIS = National Health Insurance Service in Korea, NOS = Newcastle-Ottawa Scale, OR = odds ratio, Taiwan NHIRD = Taiwan National Health Insurance Research Database.
# Reference number

achieving statistical significance. It indicates that publication bias might not be present.

4. Discussion

In the present meta-analysis involving 4 case–control studies, the OR of allopurinol exposure was 0.91 among subjects with dementia compared with controls.

The sensitivity analysis revealed that after excluding the studies with concern, the pooled OR did not achieve statistical significance. Due to the small number of eligible studies, the definite conclusion could not be drawn as to the relationship between allopurinol use and the probability of dementia. So the interpretation of our meta-analysis should be cautious. Whether the mechanisms via inhibiting xanthine oxidase and/or reducing serum uric acid could affect the probability of developing dementia need to be clarified in future research. But it is beyond the scope of our meta-analysis.

Because the chi-square test for heterogeneity showed a *P* value of .43, which was not statistically significant (shown in Fig. 2), we assumed that the true effect size was the same in all studies. That is why we used a fixed-effect model for a meta-analysis. We used the R package to calculate the power. The power analysis disclosed the overall effect sizes (OR = 0.91), the number of included studies (k = 4), the expected average sample size in cases (n1= 8320) and in controls (n2 = 30884) as well as α = 0.05. Thus, the power is 100% in this study.

The bias and limitations are discussed. First, the diagnosis of gout and dementia in the 4 eligible studies was defined by the International Classification of Diseases Ninth Revision Clinical Modification (ICD-9 codes) or International Classification of Diseases Tenth Revision Clinical Modification (ICD-10 codes). The diagnosis criteria were not available in the 4 eligible studies. Some of the dementia cases might be misclassified as the controls because they presented nonspecific manifestations of dementia. The bias of misclassification diagnosis could not be excluded. However, recall bias which was frequently found in

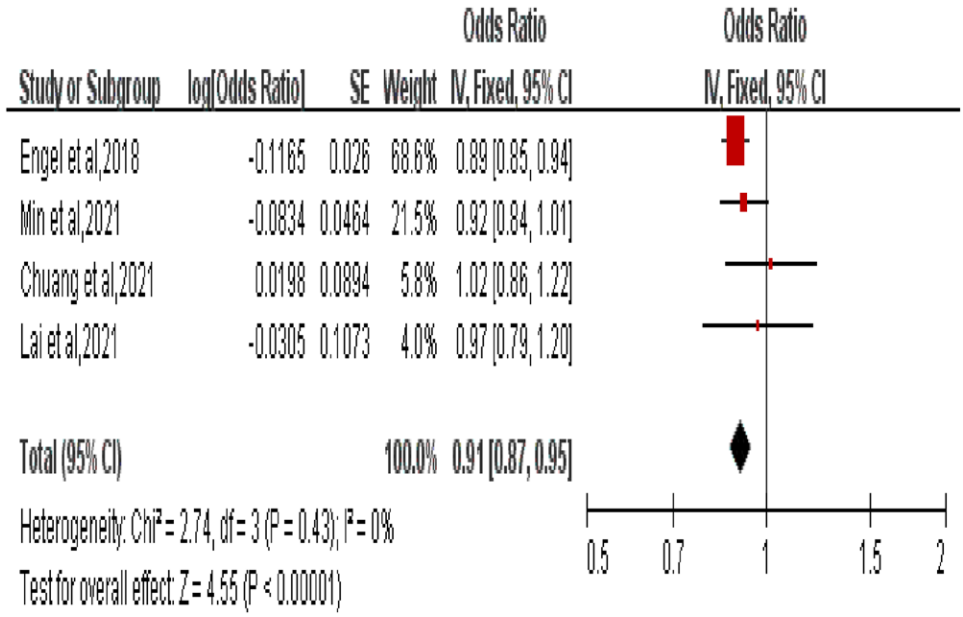

Figure 2. Fixed-effect model of the pooled odds ratio in a meta-analysis. CI = confidence interval.

a case–control design might be minimal in the 4 eligible studies. Second, gout people who received allopurinol therapy might frequently visit clinicians. So these gout people on allopurinol therapy would have a greater chance of being diagnosed with dementia if early manifestations related to dementia were presented. The prevalence of dementia could be greater in gout people on allopurinol therapy than the general population. Thus, the surveillance bias was unable to be excluded. Third, unmeasured confounding variables could be present in the 4 eligible studies. For example, alcohol intake is a key risk for gout and dementia.[20,21] Therefore, alcohol intake could be a confounder related to allopurinol exposure and dementia. Alcohol intake and other lifestyle information were not analyzed in 4 eligible studies. So confounding bias could not be excluded. Fourth, the prevalence of gout and hyperuricemia is higher in males than in females.[22] In our meta-analysis, only the study of Chuang et al[13] reported that no relationship was noted between the use of allopurinol and the probability of dementia in males and females. The other studies did not report the sex-specific estimates.[10,12,14] It points out the future research direction in sex. Fifth, due to the limitation of claims data used, the laboratory information was not available in the 4 eligible studies. The baseline serum uric acid and the degree of uric acid reduction based on the use of allopurinol could not be checked. Therefore, the risk of dementia associated with the changes in serum uric acid was unable to be explored. It points out the future research direction linking the uric acid level and the probability of dementia. Sixth, because all of the 4 eligible studies were based on claims data, the inherent limitations of claims data must exist. Currently, this issue about allopurinol exposure and the risk of dementia is unable to be clarified by the analysis of claims data. Seventh, dementia has several causes. The 4 eligible studies did not report the dementia type-specific estimates. The association between the allopurinol exposure and the type of dementia could not be examined. It points out the future research direction. Meanwhile, causality could not be established in a case–control design. We suggest that only randomized controlled trials have an opportunity to conduct good research design and fair monitoring.

5. Conclusion

This is the first meta-analysis to report that there is a negative relationship between the allopurinol exposure and the probability of dementia. Although the results favor the hypothesis, currently, it is unable to draw strong conclusions about the protective effect of allopurinol against dementia due to inclusion of only a few eligible studies and the inherent limitations of claims data. Randomized controlled trials are required to test the relationship between allopurinol exposure and the probability of dementia.

Author contributions

Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and has approved the final draft submitted. Bing-Fang Hwang, Yu-Hung Kuo, and Chiu-Shong Liu conducted data analysis. Kuan-Fu Liao interpreted the data.

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