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The risk of dementia in gout and hyperuricemia: a meta-analysis of cohort studies

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Abstract

Objectives: Gout is a systemic disease based on abnormal uric acid metabolism. Recent studies have found that elevated uric acid levels are related to the occurrence of dementia. We conducted the study to investigate the association between dementia and gout or hyperuricemia.

Design: Systematic review and meta-analysis of cohort studies.

Data sources: Studies were screened from inception to June 28, 2019 by searching Medline, EMBASE, and the Cochrane library databases.

Eligibility criteria: Cohort studies comparing the risk of dementia in patients with gout and hyperuricemia versus non-gout and non-hyperuricemia controls were enrolled.

Data extraction and analysis: Two reviewers separately selected studies and extracted data using the Medical Subject Headings without restriction in languages or countries. The adjusted HRs was pooled using the DerSimonian and Laird random-effects model. Sensitivity analyses were conducted to evaluate the stability of results. Publication bias was evaluated

with Egger's and Begg's tests. Quality assessment was estimated according to the Newcastle-Ottawa scale.

Results: A total of four cohort studies met the inclusion criteria were abstracted in our meta-analysis. We found gout and hyperuricemia do not increase the risk of dementia, with the pooled hazard ratio of 0.94 (95% CI, 0.69–1.28). While gout and hyperuricemia might decrease the risk of Alzheimer's disease (AD), with the pooled hazard ratio of 0.78 (95% CI, 0.64–0.95). Little evidence of publication bias was observed. Quality assessment of included studies was high (range from 6 to 8 stars).

Conclusions: Our study shows that gout and hyperuricemia do not increase the risk of dementia. However, gout and hyperuricemia have a protective effect on AD. Due to the limited number of research articles, more investigations are needed to demonstrate the potential relationship between dementia and gout or hyperuricemia.

Keywords: gout, hyperuricemia, dementia, Alzheimer's disease; meta-analysis;

Strengths and limitations of this study：

- We conducted a meta-analysis of cohort studies to compare the risk of dementia in patients with gout and hyperuricemia.
- Our study provides a simple indicator of prognosis management for patients with dementia as a clinical guide.
- Countries, environmental factors, ethodological factors in design, and clinical features were the main sources of heterogeneity in our study.

INTRODUCTION

With the aging of the population and the improvement of living standards, the incidence of ageing-related cerebrovascular diseases and metabolic diseases is increasing. Dementia is a mental disorder syndrome caused by various cerebrovascular diseases, which seriously endangers the health of the elderly. Notably, the number of people with dementia worldwide is expected to soar up to 115 million by 2050[1].Therefore, it is essential to study the pathogenesis of dementia so as to better prevent and treat dementia.

Recent studies reported that patients with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus might be at an increased risk of developingdementia[2 3].The association between chronic inflammation and dementia has been identified in several epidemiologic studies. Gout, the most common inflammatory arthritis in adults, is characterized by hyperuricemia and monosodiumurate crystal formation which cause chronic inflammation. Uric acid is a natural water-soluble antioxidant in the human body, which also has an oxidative effect. In recent years, blood uric acid levels have been considered closely related to cognitive function such asParkinson's disease and Alzheimer'sdisease[4].Manystudieshave evaluated the relationship between uric acid and cognitive impairment[5-9].Research conducted by Luet al.[10]supported the potential neuroprotective function of uric acid. In contract, Schretlen et al.[11]found that elevated blood uric acid increased the risk of cognitive impairment. Whether uric acid is good or bad for dementia lacks strong evidences. Our study aimed to review and summarize literature about cohort studies on the association between dementia and gout or hyperuricemia.

METHODS

A comprehensive literature search was conducted to identify all relevant articles from the inception of each database until June 28, 2019. We searched three databases, including Medline (Ovid), Embase (Ovid) and Cochrane Library. Two independent reviewers searched databases systemically and extensively to obtain the studies about the association between dementia and gout or hyperuricemia without any language or country restrictions. The Medical Subject Heading (MeSH) terms for "gout", "hyperuricemia" and "dementia" were used in the search strategy.

Data abstraction was performed by two independent reviewers who using a unified form. From each primary study we extracted the following information about the studies: first author's last name, year of publication, country where the study was performed, sample size, mean age, proportion of men, diagnostic basis, subtype of dementia, average duration of follow years, adjusted covariates, quality of assessment and adjusted hazard ratio (HR) and 95% confidence interval (CI).

A quality score was calculated to assess the quality of the studies according to the Newcastle-Ottawa scale. Three major components were collected: selection (0–4 points), Comparability (0–2 points) and Outcome (0–3 points). A higher score (at least≥5points) represents better quality.

Inclusion and exclusion criteria

All the articles were carefully read and evaluated by two investigators, and they assessed

literature eligibility independently; Articles were included in the systematic review ifthey fulfill the following criteria:(1)the study was a cohort study; (2) the authors reported data from an original, peer-reviewed study; (3)the authors reported the risk estimates of dementia morbidity in gout or hyperuricemia patients compared with non-gout or non-hyperuricemia controls; (4) adjusted hazard ratio (HR) with each study can be extracted or calculated; and (5) clearly stated dementia, gout and hyperuricemia diagnostic criteria. We used broad inclusion criteria for studies, including all types of dementia (including vascular dementia, AD et al).

Articles were considered for exclusion in the systematic review if:(1) conference articles, review articles, editorials, commentaries, hypothesis papers, letters;(2)multiple publications from the same population; (3) did not set a control group; and (4) reported associations with dementia occurring before onset of gout or hyperuricemia.

Statistical analysis

Review Manager 5.3 software was used to calculate the pooled estimate effect. The adjusted HRs was pooled using the DerSimonian and Laird random-effects model, and the weights were equal to the inverse variance of each study's effect estimation. Forest plots were produced to visually assess the HRs and corresponding 95%CIsacross studies. Heterogeneity of HRs across studies was evaluated by the Cochrane Q statistic and the I^2 statistic (values of 25%, 50% and 75% were considered to represent low, medium and high heterogeneity respectively)[12 13]. Sensitivity analysis was conducted to evaluate the stability of results. Publication bias was evaluated with Egger's and Begg's tests.

RESULTS

Details of the selection process are presented in a flow diagram (Figure 1). 740potentially relevant articles were identified from the electronic databases. After one initial screening based on titles and abstracts with the aforementioned criteria, 665 articles were excluded. Full-text evaluation was conducted in the remaining 75 articles, and 71 articles were excluded for not analyze the association of interest or irrelevant or case-control studies or review or meta-analysis or not fulfilling our inclusion criteria. Eventually, four cohort studies were ultimately selected for meta-analysis[7-9 14].

The details of the characteristics of included studies in meta-analysis were demonstrated in Table 1.All the four studies included both men and women, and the average age of participants is ≥60 years old. These studies were conducted primarily in US, USA, Taiwan, China and France. The study samples ranged from 406 to 1712821, and the follow-up durations ranged from 2.3 to 12 years. The quality of studies was good, ranging from 6 to 8 stars.

We use Egger's (P=0.41) and Begg's (P=1.00) tests to further test the publication bias, and there was no statistical evidence of a publication bias among studies. In sensitivity analysis, we evaluate it by changing the analysis model from random-effects model to fix-effects model. We found that the results were unstable for different analysis models giving different results. When use random-effects model, we found that gout or hyperuricemia does not increase the risk of dementia, with the pooled hazard ratio of 0.94 (95% CI, 0.69–1.28).When use fix-effects model, we found that gout or hyperuricemia increase the risk of dementia, with the pooled hazard ratio of 1.07 (95% CI, 1.04–1.10). In consideration of the high

heterogeneity of the included articles, we prefer the results given by the random-effects model.

In our study of meta-analysis, we found that it did not increase the risk of dementia among patients with gout or hyperuricemia, with the pooled hazard ratio of 0.94 (95% CI, 0.69–1.28), with an I^2 of 98%, $P < 0.001$(Figure 2). While there is a decreased risk of AD in gout or hyperuricemia, with the pooled hazard ratio of 0.78 (95% CI, 0.64–0.95), with an I^2 of 55%, P=0.01(Figure 3).The reasons for high heterogeneity are considered to be related to differences in countries, environmental factors, methodological factors in design, and clinical features et al.

DISCUSSION

This meta-analysis is based on cohort studies in different countries, thus provide a comprehensive evaluation on the association between dementia and gout or hyperuricemia. All studies were assessed high quality by Newcastle–Ottawa Scale. The included studies had adjustments for other risk factors.Our meta-analysis showed no statistically significant risk of dementia in patients with gout or hyperuricemia compared with non-gout or non-hyperuricemia controls. By contrast, gout or hyperuricemia is negatively correlated with the risk of AD. The existing researches hold different views on the pathophysiological mechanism of the relationship between gout and dementia. Whether the level of high uric acid has protective or harmful effects on dementia has not been uniformly summarized.

Several studies indicated that inflammatory pathways may play an important role in increasing the risk of dementia[15 16]. Autoimmune disease, as a chronic disorder, has been

suggested that be associated with the incidence of dementia. Scientists suggested that systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS)also have a higher risk of dementia[3] [17-20].Moreover, an 13-year, nationwide, population-based retrospective cohort study showed that patients with Sjogren's syndrome (SS) have a higher risk of dementia[21] [22].But there is no unified conclusion about the relationship between dementia and gout or hyperuricemia, which is the original intention of our meta-analysis study.

Recently there is still controversy about whether gout or hyperuricemia and dementia are related. There are several speculations about the mechanism of gout affecting the onset of dementia. Some scholars believe that gout or hyperuricemia may increase the risk of dementia[8] [14]because of chronic inflammation from gout has some effect on the brain. Some studies suggested that high inflammatory cytokines levels in brains with neurodegeneration play important roles in the pathogenesis of dementia[23-25].Otherssuggested that gout is associated with oxidative stress, which may play a key role in the pathogenesis of dementia[26] [27]. Besides, elevated inflammatory cytokines could damage endothelial cell, activate inflammatory cells, and cause oxidative stress, which promoted the progression of atherosclerosis[24] [28].Atherosclerotic cardiovascular diseases are well-established risk factors for dementia[29].Additionally, some evidence show that the association of hyperuricemia with cardiovascular disease is due to concomitant oxidative stress[30]. In conclusion, chronic inflammation and oxidative stress may be the final pathway in dementia and gout or hyperuricemia, which may explain the high risk of dementia in elderly people with gout or hyperuricemia.

On the contrary, some scholars confirm that gout or hyperuricemia may decrease the risk of

dementia[7 9].Uric acid was proposed to have both a pro-oxidant effect[31]and an anti-oxidant effect[32 33].Uric acid is an antioxidant and metal chelator properties in vitro[34 35], could effectively clear peroxynitrite and hydroxyl radicals[32 36 37] and reduce oxidative stress as an antioxidant, may exert possible neuroprotective effects. What's more, it is reported that pathogenesis of AD is related to mitochondrial dysfunction. Some studies showed that uric acid might preserve mitochondrial function and suppress oxyradical accumulation[32],thus inhibiting cytotoxic activity of lactoperoxidase[38] and repairing free radical-induced DNA damage[39].In our study, we analyzed the AD subgroup of dementia and found that gout can reduce the risk of AD. It might also confirm the neuroprotective role of uric acid.

Our study found that there is no correlation between dementia and gout or hyperuricemia. Dementia has variable clinical symptoms, multiple subtypes, and complex pathogenesis, which may explain the contradictory results of studies on gout or hyperuricemia. More researches are needed to support the viewpoint. The risk of AD is inversely proportional to gout, and the neuroprotective mechanism of uric acid may play a dominant role in the pathogenesis of AD.

However, there are some potential limitations exist in our study. Firstly, there are four studies in our meta-analysis, whose number of articles included is relatively small. Besides, cohort studies were mostly medical registry-based studies, which would raise a concern over coding inaccuracy and misclassification. Secondly, although studies included had been adjusted for other risk factors, the statistical heterogeneity was high, which might attribute to differences in countries, environmental factors, ethodological factors in design, and clinical features. Thirdly, this is a pooled analysis of observational studies, which can only demonstrate an

association but not causality. Therefore, we cannot determine the impact of gout or hyperuricemia or other unknown confounding factors on the outcome of dementia risk. What's more, in sensitivity analysis, we found that the results were unstable by using different analysis models. Considering the high heterogeneity of the included articles, we prefer the results given by the random-effects model. As mentioned before, they call for caution in interpreting the present meta-analysis findings.

Our meta-analysis of cohort studies suggests that there is no risk of dementia among patients with gout and hyperuricemia. However, high uric acid levels have a protective effect on Alzheimer's disease. More investigations are needed to demonstrate the potential relationship between dementia and patients with gout and hyperuricemia.

Contributiors Conceptualization: YL. Methodology: S-YP and R-JC. Formal analysis: Z-JX; Data curation: Q-PZ. Writing original draft preparation: S-YP and R-JC. Writing - review and editing: YL. Approval of final manuscript: all authors.

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Competing interests None declared.

Patient and public involvement No patient involved.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Table 1 Characteristics of included studies in the meta-analysis.

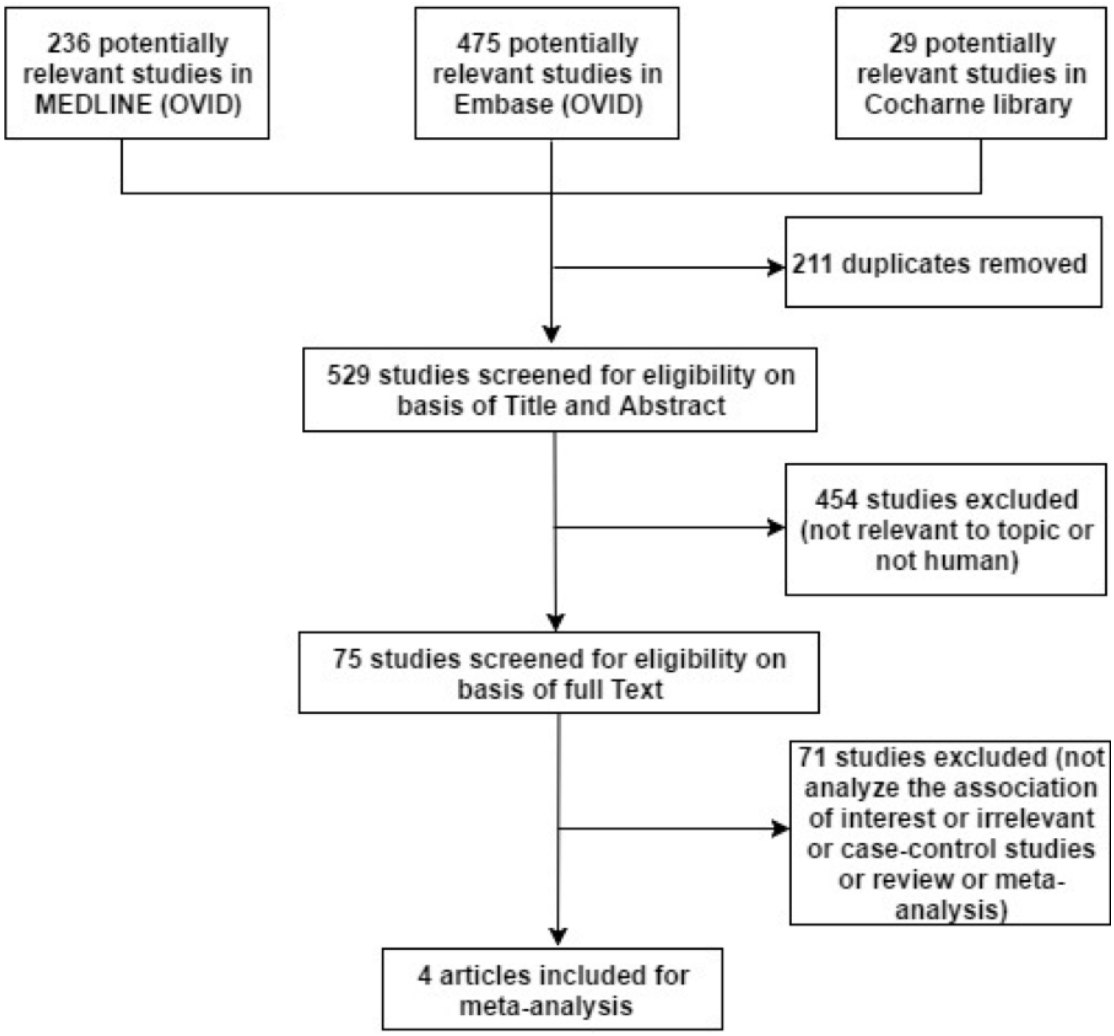
	Lu N et al. [7]	LatourteA et al. [8]	Hong JY et al. [9]	Singh JA et al.[14]
Country	UK	USA	Taiwan, China	France
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Year	2016	2018	2015	2018
Age, mean years	65	75.2	63.5	72.9
Male, %	71	42.6	63	38.7
Diagnosis of gout or Hyperuricemia	diagnostic code using the Read classification	(ICD-9-CM) codes	(ICD9-CM) codes	Hyperuricemia: ≥360 μmol/L for men, ≥300 μmol/L for women.
Diagnosis of dementia	AD diagnostic codes	(ICD-9-CM) codes	(ICD9-CM) codes	DSM-IV
Subtype of dementia	AD	All subtypes of dementia	All subtypes of dementia AD、VD	All subtypes of dementia AD
number of dementia (cases vs controls)	309/1942	5310/106346	1214/5905	32/78
Adjusted confounders	age, sex, entry-time, BMI, smoking, alcohol use, physician visits, social deprivation index, comorbidities and medication use.	age, sex, race, medical comorbidities, common medications for cardiac diseases and gout.	Age, sex, relevant comorbidities.	adjusted for age, gender, tobacco and alcohol consumption, cholesterol, medical comorbidities, medication use
Follow-up years (mean or mean±SD)	5	2.3 (1.7)	4.3(2.1)	12
Quality grading	7 stars	6 stars	7 stars	8 stars

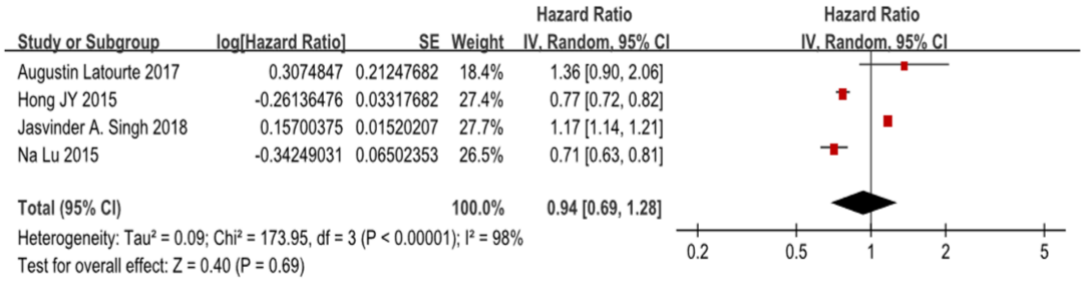
(AD: Alzheimer's disease; VD: Vascular dementia; DSM-IV: diagnostic and Statistical Manual of Mental disorders Version IV; BMI: body mass index)

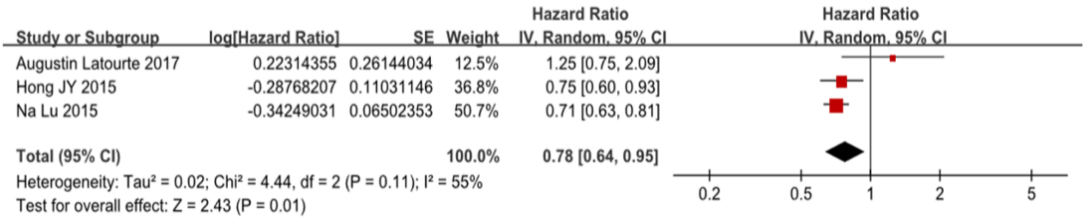
Figure 1 Flow diagram showing the identification and selection of cohort studies included in the review.

Figure 2 Forest plot showing an association between dementia and patient's with gout and hyperuricemia

Figure 3 Forest plot showing an association between AD and patient's with gout and hyperuricemia







PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	none
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P10

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The risk of dementia in gout and hyperuricemia: A meta-analysis of cohort studies

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Abstract

Objectives: Gout, characterized by hyperuricemia with monosodium urate crystal formation and inflammation, is the most common inflammatory arthritis in adults. Recent studies have found that elevated uric acid levels are related to the occurrence of dementia. We conducted a

study to investigate the association between dementia and gout or hyperuricemia.

Design: Systematic review and meta-analysis of cohort studies

Data sources: Studies were screened from inception to June 28, 2019, by searching Medline, EMBASE, and the Cochrane library databases.

Eligibility criteria: Cohort studies comparing the risk of dementia in patients with gout and hyperuricemia versus non-gout and non-hyperuricemia controls were enrolled.

Data extraction and analysis: Two reviewers separately selected studies and extracted data using the Medical Subject Headings without restriction on languages or countries. The adjusted hazard ratios (HRs) were pooled using the DerSimonian and Laird random-effects model. Sensitivity analyses were conducted to evaluate the stability of the results. Publication bias was evaluated using Egger's and Begg's tests. Quality assessment was performed according to the Newcastle–Ottawa scale.

Results: Four cohort studies that met the inclusion criteria were included in our meta-analysis. We found that gout and hyperuricemia did not increase the risk of dementia, with a pooled HR of 0.94 (95% CI, 0.69, 1.28), but might decrease the risk of Alzheimer's disease (AD), with a pooled hazard ratio of 0.78 (95% CI, 0.64, 0.95). There was little evidence of publication bias. Quality assessment of the included studies was high (range, 6–8 points).

Conclusions: Our study shows that gout and hyperuricemia do not increase the risk of dementia. However, gout and hyperuricemia might have a protective effect against AD. Due to the limited number of research articles, more investigations are needed to demonstrate the potential relationship between dementia and gout or hyperuricemia.

Keywords: Alzheimer's disease; dementia; gout; hyperuricemia; meta-analysis

Strengths and limitations of this study:

- We conducted a meta-analysis of cohort studies to compare the risk of dementia in patients with gout and hyperuricemia.
- As there are few meta-analyses of cohort studies on dementia and gout, our research provides a basis for future research.
- The results of our meta-analysis should be interpreted with caution due to the small number and high heterogeneity of the included studies.
- Differences in countries, environmental factors, and clinical features, and lack of uniformity in study designs, inclusion criteria, and follow-up durations were the main sources of heterogeneity in our study.

INTRODUCTION

With the aging of the population and the improvement in living standards, the incidence of ageing-related cerebrovascular diseases and metabolic diseases is increasing. Dementia is a common age-dependent disorder characterized by progressive deterioration of cognitive ability and function, which can be caused by primary neurologic, neuropsychiatric, and other conditions, such as traumatic brain injury and tumors. Most senile dementias are caused by neurodegeneration. Common diseases include Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal degeneration, and Parkinson's disease.[1] Notably, the number of patients with dementia worldwide is expected to increase to 115 million by 2050.[2]

Therefore, it is essential to study the pathogenesis of dementia to improve prevention and treatment of this condition.

With changes in diet and increases in obesity, the incidence of hyperuricemia also continues to rise. Hyperuricemia is caused by increased production of uric acid in and/or decreased excretion of uric acid from the body.[3] Hyperuricemia may not cause obvious clinical symptoms for a long time, but with a persistent increase in blood uric acid levels, urate deposition may occur, which can damage tissues and internal organs. In fact, hyperuricemia not only causes gout, but is also an independent risk factor for cardiovascular disease and chronic kidney disease.[4] Gout is the most common inflammatory arthritis in adults. Common hallmarks of gout include hyperuricemia, monosodiumurate crystal formation, and gouty arthritis.

Moreover, several epidemiological studies have reported an association between chronic inflammation and dementia. In recent years, blood uric acid levels have been considered to be closely related to neurodegenerative changes in Parkinson's disease and Alzheimer's disease (AD).[5] Many studies have evaluated the relationship between uric acid and cognitive impairment disorders.[6-10] The findings of Lu et al.[8] supported the potential neuroprotective function of uric acid. In contrast, Schretlen et al.[11]found that elevated blood uric acid levels increased the risk of cognitive impairment. Thus, whether uric acid predisposes to or protects against dementia remains unclear.

Thus, we here performed a systematic review and meta-analysis of the data reported by cohort studies on the association between dementia and gout or hyperuricemia.

METHODS

A comprehensive literature search was conducted to identify all relevant articles in the Medline (Ovid), Embase (Ovid), and Cochrane Library databases, from their respective inception dates until June 28, 2019. Two independent reviewers searched the databases systemically and extensively to obtain studies about the association between dementia and gout or hyperuricemia, without any language or country restrictions. The Medical Subject Heading (MeSH) terms "gout", "hyperuricemia," and "dementia" were used in the search strategy.

Data abstraction was performed by two independent reviewers using a unified form. From each primary study, we extracted the following information: the first author's last name, year of publication, country where the study was performed, sample size, mean age, proportion of men, diagnostic criteria, subtype of dementia, average duration of follow-up years, adjusted covariates, quality of assessment, and adjusted hazard ratio (HR) and 95% confidence interval (CI).

The quality of the studies was scored according to the Newcastle-Ottawa scale, where a higher score (≥5 points) represents better quality. Three major components were scored: selection (0–4 points), comparability (0–2 points), and outcome (0–3 points).

Inclusion and exclusion criteria

Two investigators read the title and abstracts of all identified papers and evaluated the literature eligibility independently. Then, we obtained full reports from the articles that appeared eligible, and two investigators again independently assessed whether the papers met

the following inclusion criteria: (1) cohort study; (2) original, peer-reviewed study; (3) risk estimates of dementia morbidity in gout or hyperuricemia patients compared with non-gout or non-hyperuricemia controls, with dementia occurring after gout or hyperuricemia; (4) adjusted hazard ratio (HR) can be extracted or calculated; and (5) clearly stated dementia (any type, including vascular dementia and AD), gout, and hyperuricemia diagnostic criteria; and (6) if multiple studies were reported from the same center and using the same patient population, we selected the study with the largest sample size or with the most comprehensive data for the meta-analysis. The following reports were excluded: (1) conference articles, review articles, editorials, commentaries, hypothesis papers, case reports, and letters; (2) multiple publications from the same population; (3) studies without a control group; (4) studies without clear definition of hyperuricemia, gout, or dementia; (5) studies with dementia occurring before the onset of gout or hyperuricemia.

Statistical analysis

Review Manager 5.3 software was used to calculate the pooled effect size estimate. The adjusted hazard ratios (HRs) were pooled using the DerSimonian and Laird random-effects model, and the weights were equal to the inverse variance of each study's effect estimation. Forest plots were produced for visual assessment of the HRs and corresponding 95% CIs across studies. Heterogeneity of HRs across studies was evaluated using the Cochrane Q statistic and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively).[12 13] Sensitivity analysis was conducted to evaluate the stability of the results. Publication bias was evaluated using Egger's and Begg's

tests.

RESULTS

A flow diagram of the selection process is presented in Figure 1. A total of 740 potentially relevant articles were identified by keyword search from the electronic databases. After the initial screening based on titles and abstracts, 665 articles were excluded. Full-text evaluation was conducted in the remaining 75 articles, and 71 articles were excluded due to irrelevant topics or because of being case–control, review, or meta-analysis reports, or because of not fulfilling our inclusion criteria. Ultimately, four cohort studies were selected for the meta-analysis.[8-10 14]

The characteristics of the included studies are shown in Table 1. All four studies included both men and women, and the average age of participants was ≥ 60 years. These studies were conducted primarily in the UK, USA, Taiwan, China, and France. The study samples ranged from 406 to 1,712,821, and the follow-up durations ranged from 2.3 to 12 years. 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.The quality of studies was good, ranging from 6 to 8 points.

We used Egger's (P = 0.41) and Begg's (P = 1.00) tests to test the publication bias, and there was no statistical evidence of publication bias among the studies. We performed a sensitivity analysis by changing the analysis model from a random-effects model to a fixed-effects model, and found that the results were unstable for different analysis models, giving different

results. When using the random-effects model, we found that gout or hyperuricemia did not increase the risk of dementia, with a pooled hazard ratio of 0.94 (95% CI, 0.69, 1.28). Using the fixed-effects model, we found that gout or hyperuricemia increased the risk of dementia, with a pooled hazard ratio of 1.07 (95% CI, 1.04, 1.10). In consideration of the high heterogeneity of the included articles, we preferred the results given by the random-effects model.

In our meta-analysis, we found no increased risk of dementia among patients with gout or hyperuricemia, with a pooled hazard ratio of 0.94 (95% CI, 0.69, 1.28), with an I^2 of 98%, $P < 0.001$(Figure 2). However, there was a decreased risk of AD in patients with gout or hyperuricemia, with a pooled hazard ratio of 0.78 (95% CI, 0.64, 0.95), with an I^2 of 55%, $P = 0.01$ (Figure 3).

Lu et al. and Latourte et al. analyzed dementia patients in European, Singh et al. analyzed patients in North America, and Hong et al. investigated data of Asian populations. Lu et al. used AD diagnostic codes, which were positively predicted at 83% in a UK-based GPRD-based validation study. Singh et al. and Hong et al. used ICD9-CM as the diagnostic criterion for dementia. Latourte et al. used the DSM-IV criteria for the diagnosis of dementia and NINCDS-ADRDA as the diagnostic standard for AD. We consider that the reasons for the high degree of heterogeneity are related to the differences between races, diets, climate factors, clinical characteristics between different countries, lack of standardized design, inclusion criteria, and uniform follow-up time, which may affect the final results universality.

DISCUSSION

This meta-analysis was based on four articles of cohort studies performed in different

countries, thus providing a comprehensive evaluation of the association between dementia and gout or hyperuricemia. The four cohort studies analyzed 121,136 cases of dementia, of which Lu et al. included only patients with AD, while the other three analyzed data on all types of dementia. In addition, of the four articles included in our meta-analysis, only one described a lower risk of developing vascular dementia (VD) in patients with gout. All studies were assessed as being of high quality based on the Newcastle–Ottawa Scale. The included studies had adjustments for other risk factors. Our meta-analysis showed no statistically significant risk of dementia in patients with gout or hyperuricemia compared with the non-gout or non-hyperuricemia controls. In contrast, gout or hyperuricemia was negatively correlated with the risk of AD.

The existing reports hold different views on the pathophysiological mechanism of the relationship between gout and dementia. Whether a high uric acid level has predisposes to or protects against dementia has not been uniformly summarized. Several studies have indicated that inflammatory pathways may play an important role in increasing the risk of dementia.[15 16] Hyperuricemia causes persistent low-grade systemic inflammation of gout and can also affect the inflammatory capacity of immune cells.[17] However, there has been no unified conclusion about the relationship between dementia and gout or hyperuricemia, which prompted our meta-analysis.

To date, it has been controversial whether gout or hyperuricemia and dementia are related. There have been several speculations about the mechanism by which gout could affect the onset of dementia. Some reports propose that gout or hyperuricemia may increase the risk of dementia[9,14] because chronic inflammation from gout has some effects on the brain. Some

studies have suggested that high inflammatory cytokine levels in brains with neurodegeneration play important roles in the pathogenesis of dementia.[18-20] Others have suggested that gout is associated with oxidative stress, which may play a key role in the pathogenesis of dementia.[21,22] Elevated inflammatory cytokines can damage endothelial cells, activate inflammatory cells, and cause oxidative stress, which promotes the progression of atherosclerosis.[19 23] Atherosclerotic cardiovascular diseases are well-established risk factors for dementia.[24] Additionally, there has been some evidence that an association of hyperuricemia with cardiovascular disease is due to concomitant oxidative stress.[25] In addition, Mollenhauer et al. compared 135 new-onset PD patients with 109 healthy people and found that elevated uric acid levels could predict the cognitive decline in Parkinson's disease.[5] Taken together, chronic inflammation and oxidative stress may be the final pathways in dementia and gout or hyperuricemia, which may explain the high risk of dementia reported by some studies in elderly people with gout or hyperuricemia.

In contrast, some studies have confirmed that gout or hyperuricemia may decrease the risk of dementia.[8 10] Uric acid has been proposed to have both a pro-oxidant effect[26] and an anti-oxidant effect.[27,28] It can have some pro-oxidant effects in its oxidized state, but there is relatively little evidence that this is an important mechanism for circulating uric acid, in comparison to its antioxidant role. Uric acid is well established as an important circulating antioxidant and free-radical scavenger. It is an antioxidant and metal chelator in vitro.[29 30] It can effectively clear peroxynitrite and hydroxyl radicals[27 31 32] and reduce oxidative stress as an antioxidant, may exert possible neuroprotective effects. Moreover, it has been reported that the pathogenesis of AD is related to mitochondrial dysfunction. Some studies have shown that

uric acid might preserve mitochondrial function and suppress oxyradical accumulation;[27] thereby inhibiting the cytotoxic activity of lactoperoxidase[33] and repairing free radical-induced DNA damage.[34] In our study, we analyzed the AD subgroup of dementia and found that gout can reduce the risk of AD. This may also confirm the neuroprotective role of uric acid.

Our study found no correlation between dementia and gout or hyperuricemia. Dementia involves variable clinical symptoms, multiple subtypes, and complex pathogenesis, which may explain the contradictory results of studies on gout or hyperuricemia. More research is needed to support this viewpoint. The risk of AD is inversely proportional to gout, and the neuroprotective mechanism of uric acid may play a dominant role in the pathogenesis of AD.

However, there were some potential limitations to our study. First, there were only four studies in our meta-analysis, whose number of articles included were relatively small. Moreover, the cohort studies were mostly medical registry-based studies, which would raise concerns over coding inaccuracy and misclassification. Second, although studies included had been adjusted for other risk factors, the statistical heterogeneity is still high, which might be attributed to differences in demographics, dietary factors, environmental factors, and clinical characteristics in different countries, or lack of standardized design, inclusion criteria, and follow-up time. Third, this was a pooled analysis of observational studies, which could only demonstrate an association, but not causality. Therefore, we cannot determine the impact of gout, hyperuricemia, or other unknown confounding factors on the outcome of dementia risk. Moreover, in the sensitivity analysis, we found that the results were unstable when using different analysis models. Considering the high heterogeneity of the included articles, we

preferred the results given by the random-effects model. Consequently, caution is needed when interpreting the present meta-analysis findings.

In conclusion, our meta-analysis of cohort studies suggested that there is no risk of dementia among patients with gout and hyperuricemia. However, high uric acid levels have a protective effect on AD. More investigations are needed to demonstrate the potential relationship between dementia and patients with gout and hyperuricemia.

Contributors Conceptualization: YL Methodology: S-YP and R-JC. Formal analysis: Z-JX; data curation: Q-PZ. Writing original draft preparation: S-YP and R-JC. Writing review and editing: YL. Approval of final manuscript: All authors

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Table 1 Characteristics of included studies in the meta-analysis.

	Lu N et al. [8]	Singh JA et al.[14]	Hong JY et al. [10]	Latourte A et al. [9]
Country	UK	USA	Taiwan, China	France
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Year	2016	2018	2015	2018
Age, mean years	65	75.2	63.5	72.9
Male, %	71	42.6	63	38.7
Diagnosis of gout or Hyperuricemia	diagnostic code using the Read classification	(ICD-9-CM) codes	(ICD9-CM) codes	Hyperuricemia: ≥360 μmol / L for men, ≥300 μmol / L for women.
Diagnosis of dementia	AD diagnostic codes	(ICD-9-CM) codes	(ICD9-CM) codes	DSM-IV NINCDS-ADRDA
Subtype of dementia	AD	All subtypes of dementia	All subtypes of dementia AD、VD	All subtypes of dementia AD
Number of dementia with controls	309/238805	106346/1416173	5905/114742 AD:102/114742 VD:210/114742	78/1192 AD:55/1192
Number of dementia with cases	1942/59224	5310/296648	1214/28769 AD:542/28769 VD:991/28769	32/406 AD:21/406
Adjusted confounders	Age, gender, entry-time, BMI, smoking, alcohol use, physician visits, social deprivation index, comorbidities, and medication use.	Age, gender, race, medical comorbidities, common medications for cardiac diseases, and gout.	Age, gender, relevant comorbidities.	Age, gender, tobacco and alcohol consumption, cholesterol, medical comorbidities, medication use

Follow-up years (mean or mean ± SD)	5	2.3 (1.7)	4.3(2.1)	12
Quality grading	7 points	6 points	7 points	8 pionts

(AD: Alzheimer's disease; VD: Vascular dementia; DSM-IV: Diagnostic and Statistical Manual of Mental disorders Version IV; NINCDS-ADRDA: the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; ICD9-CM: International Classification of Diseases Ninth Revision, Clinical Modification codes; BMI: body mass index)

Figure 1 Flow diagram showing the identification and selection of cohort studies included in the review.

Figure 1

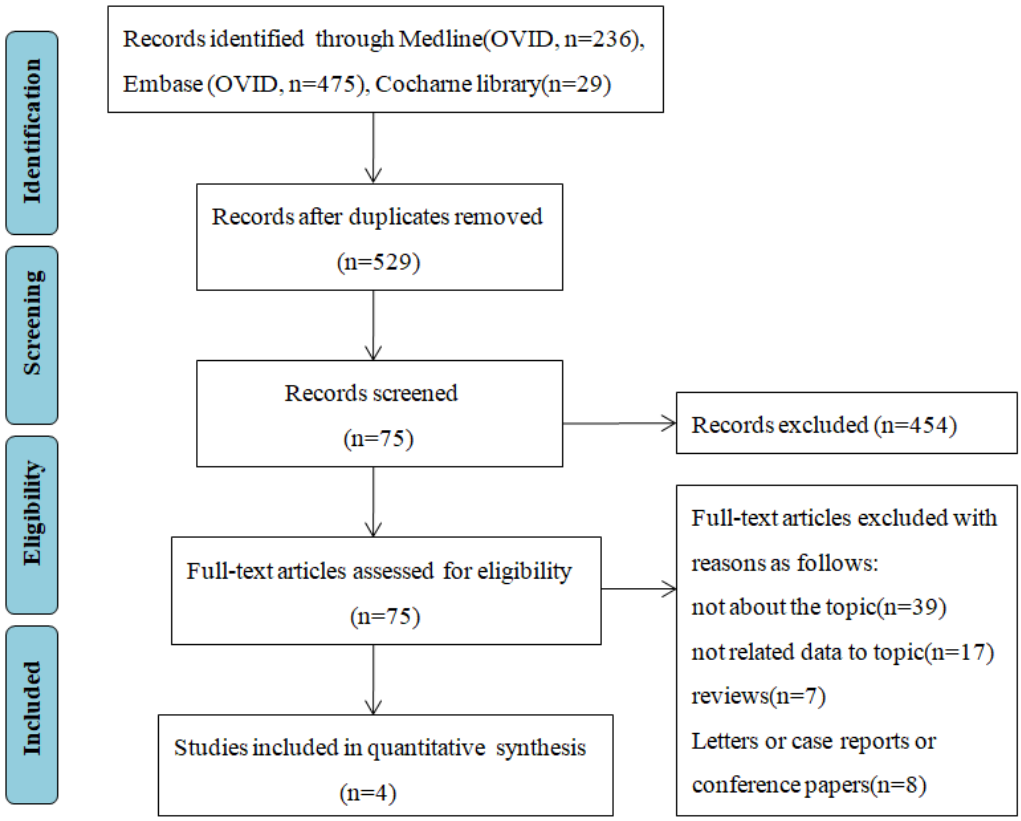


Figure 2 Forest plot showing an association between dementia and patient's with gout and hyperuricemia.

Figure 2

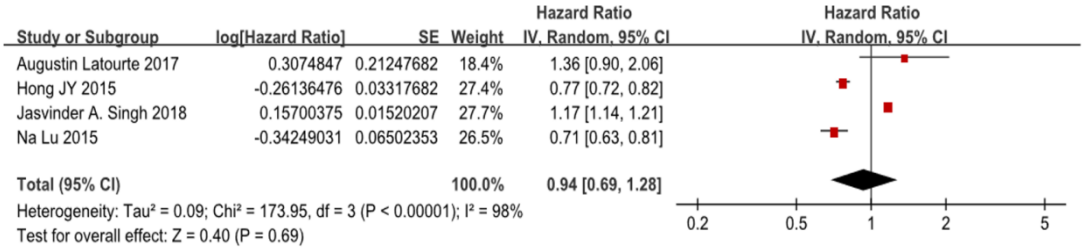
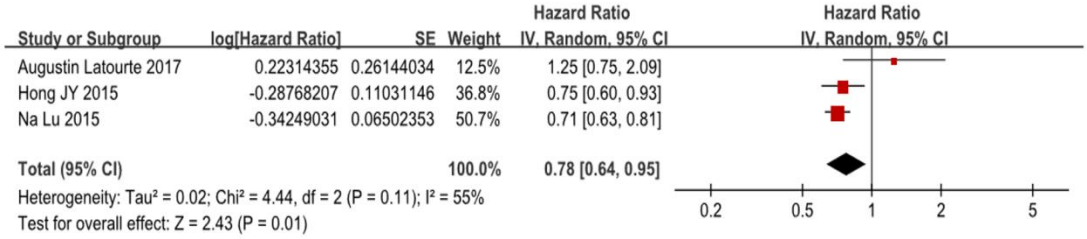


Figure 3 Forest plot showing an association between AD and patient's with gout and hyperuricemia.

Figure 3



Appendix 1

Medline Ovid Search Strategy

1. exp Dementia/

2. Delirium/

3. Wernicke Encephalopathy/

4. Delirium, Dementia, Amnestic, Cogni-tive Disorders/

5. dement*.mp.

6. alzheimer*.mp.

7. (lewy* adj2 bod*).mp.

8. deliri*.mp.

9. (chronic adj2 cerebrovascular).mp.

10. (organic brain disease or organicbrain syndrome).mp

11. (normal pressure hydrocephalus andshunt*).mp.

12. benign senescent forgetfulness.mp.

13. (cerebr* adj2 deteriorat*).mp.

14. (cerebral* adj2 insufficient*).mp.

15. (pick* adj2 disease).mp.

16. (creutzfeldt or jcd or cjd).mp.

17. huntington*.mp.

18. binswanger*.mp.

19. korsako*.mp.

20.1-19/OR

21.exp gout/

22.gout.mp.

23. exp hyperuricemia /

24. uric acid.mp.

25.20-23/OR

26. 20 and 25

Appendix 2

Embase search strategy

1.exp gout/

2.gout.mp.

3. exp hyperuricemia /

4. uric acid.mp.

5.1-4/OR

6. exp *dementia/

7. dement*.ti,ab.

8. alzheimer*.ti,ab.

9. (lewy* adj2 bod*).ti,ab.

10. (frontotemporal* or FTD or FTLD).ti,ab.

11.6-10/or

12. 5 and 11

Appendix 3

Cochrane librarysearch strategy

1.exp gout/

2.gout.mp.

3. exp hyperuricemia /

4. uric acid.mp.

5.1-4/OR

6. exp *dementia/

7. dement*.ti,ab.

8. alzheimer*.ti,ab.

9. (lewy* adj2 bod*).ti,ab.

10. (frontotemporal* or FTD or FTLD).ti,ab.

11.6-10/or

12. 5 and 11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	none
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The risk of dementia in gout and hyperuricemia: A meta-analysis of cohort studies

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Word count: 4211 words

Abstract

Objectives: Gout, characterized by hyperuricemia with monosodium urate crystal formation and inflammation, is the most common inflammatory arthritis in adults. Recent studies have found that elevated uric acid levels are related to the occurrence of dementia. We conducted a

study to investigate the association between dementia and gout or hyperuricemia.

Design: Systematic review and meta-analysis of cohort studies

Data sources: Studies were screened from inception to June 28, 2019, by searching Medline, EMBASE, and the Cochrane library databases.

Eligibility criteria: Cohort studies comparing the risk of dementia in patients with gout and hyperuricemia versus non-gout and non-hyperuricemia controls were enrolled.

Data extraction and analysis: Two reviewers separately selected studies and extracted data using the Medical Subject Headings without restriction on languages or countries. The adjusted hazard ratios (HRs) were pooled using the DerSimonian and Laird random-effects model. Sensitivity analyses were conducted to evaluate the stability of the results. Publication bias was evaluated using Egger's and Begg's tests. Quality assessment was performed according to the Newcastle–Ottawa scale.

Results: Four cohort studies that met the inclusion criteria were included in our meta-analysis. We found that gout and hyperuricemia did not increase the risk of dementia, with a pooled HR of 0.94 (95% CI, 0.69, 1.28), but might decrease the risk of Alzheimer's disease (AD), with a pooled hazard ratio of 0.78 (95% CI, 0.64, 0.95). There was little evidence of publication bias. Quality assessment of the included studies was high (range, 6–8 points).

Conclusions: Our study shows that gout and hyperuricemia do not increase the risk of dementia. However, gout and hyperuricemia might have a protective effect against AD. Due to the limited number of research articles, more investigations are needed to demonstrate the potential relationship between dementia and gout or hyperuricemia.

Keywords: Alzheimer's disease; dementia; gout; hyperuricemia; meta-analysis

Strengths and limitations of this study:

- We conducted a meta-analysis of cohort studies to compare the risk of dementia in patients with gout and hyperuricemia.
- As there are few meta-analyses of cohort studies on dementia and gout, our research provides a basis for future research.
- The results of our meta-analysis should be interpreted with caution due to the small number and high heterogeneity of the included studies.
- Differences in countries, environmental factors, and clinical features, and lack of uniformity in study designs, inclusion criteria, and follow-up durations were the main sources of heterogeneity in our study.

INTRODUCTION

With the aging of the population and the improvement in living standards, the incidence of ageing-related cerebrovascular diseases and metabolic diseases is increasing. Dementia is a common age-dependent disorder characterized by progressive deterioration of cognitive ability and function, which can be caused by primary neurologic, neuropsychiatric, and other conditions, such as traumatic brain injury and tumors. Most senile dementias are caused by neurodegeneration. Common diseases include Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal degeneration, and Parkinson's disease.[1] Notably, the number of patients with dementia worldwide is expected to increase to 115 million by 2050.[2]

Therefore, it is essential to study the pathogenesis of dementia to improve prevention and treatment of this condition.

With changes in diet and increases in obesity, the incidence of hyperuricemia also continues to rise. Hyperuricemia is caused by increased production of uric acid in and/or decreased excretion of uric acid from the body.[3] Hyperuricemia may not cause obvious clinical symptoms for a long time, but with a persistent increase in blood uric acid levels, urate deposition may occur, which can damage tissues and internal organs. In fact, hyperuricemia not only causes gout, but is also an independent risk factor for cardiovascular disease and chronic kidney disease.[4] Gout is the most common inflammatory arthritis in adults. Common hallmarks of gout include hyperuricemia, monosodiumurate crystal formation, and gouty arthritis.

Moreover, several epidemiological studies have reported an association between chronic inflammation and dementia. In recent years, blood uric acid levels have been considered to be closely related to neurodegenerative changes in Parkinson's disease and Alzheimer's disease (AD).[5] Many studies have evaluated the relationship between uric acid and cognitive impairment disorders.[6-10] The findings of Lu et al.[8] supported the potential neuroprotective function of uric acid. In contrast, Schretlen et al.[11]found that elevated blood uric acid levels increased the risk of cognitive impairment. Thus, whether uric acid predisposes to or protects against dementia remains unclear.

Thus, we here performed a systematic review and meta-analysis of the data reported by cohort studies on the association between dementia and gout or hyperuricemia.

METHODS

A comprehensive literature search was conducted to identify all relevant articles in the Medline (Ovid), Embase (Ovid), and Cochrane Library databases, from their respective inception dates until June 28, 2019. Two independent reviewers searched the databases systemically and extensively to obtain studies about the association between dementia and gout or hyperuricemia, without any language or country restrictions. The Medical Subject Heading (MeSH) terms "gout", "hyperuricemia," and "dementia" were used in the search strategy.(See supplementary files 1)

Data abstraction was performed by two independent reviewers using a unified form. From each primary study, we extracted the following information: the first author's last name, year of publication, country where the study was performed, sample size, mean age, proportion of men, diagnostic criteria, subtype of dementia, average duration of follow-up years, adjusted covariates, quality of assessment, and adjusted hazard ratio (HR) and 95% confidence interval (CI).

The quality of the studies was scored according to the Newcastle-Ottawa scale, where a higher score (≥5 points) represents better quality. Three major components were scored: selection (0–4 points), comparability (0–2 points), and outcome (0–3 points).

Inclusion and exclusion criteria

Two investigators read the title and abstracts of all identified papers and evaluated the literature eligibility independently. Then, we obtained full reports from the articles that appeared eligible, and two investigators again independently assessed whether the papers met

the following inclusion criteria: (1) cohort study; (2) original, peer-reviewed study; (3) risk estimates of dementia morbidity in gout or hyperuricemia patients compared with non-gout or non-hyperuricemia controls, with dementia occurring after gout or hyperuricemia; (4) adjusted hazard ratio (HR) can be extracted or calculated; and (5) clearly stated dementia (any type, including vascular dementia and AD), gout, and hyperuricemia diagnostic criteria; and (6) if multiple studies were reported from the same center and using the same patient population, we selected the study with the largest sample size or with the most comprehensive data for the meta-analysis. The following reports were excluded: (1) conference articles, review articles, editorials, commentaries, hypothesis papers, case reports, and letters; (2) multiple publications from the same population; (3) studies without a control group; (4) studies without clear definition of hyperuricemia, gout, or dementia; (5) studies with dementia occurring before the onset of gout or hyperuricemia.

Statistical analysis

Review Manager 5.3 software was used to calculate the pooled effect size estimate. The adjusted hazard ratios (HRs) were pooled using the DerSimonian and Laird random-effects model, and the weights were equal to the inverse variance of each study's effect estimation. Forest plots were produced for visual assessment of the HRs and corresponding 95% CIs across studies. Heterogeneity of HRs across studies was evaluated using the Cochrane Q statistic and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively).[12 13] Sensitivity analysis was conducted to evaluate the stability of the results. Publication bias was evaluated using Egger's and Begg's

tests.

RESULTS

A flow diagram of the selection process is presented in Figure 1. A total of 740 potentially relevant articles were identified by keyword search from the electronic databases. After the initial screening based on titles and abstracts, 665 articles were excluded. Full-text evaluation was conducted in the remaining 75 articles, and 71 articles were excluded due to irrelevant topics or because of being case–control, review, or meta-analysis reports, or because of not fulfilling our inclusion criteria. Ultimately, four cohort studies were selected for the meta-analysis.[8-10 14]

The characteristics of the included studies are shown in Table 1. All four studies included both men and women, and the average age of participants was ≥ 60 years. These studies were conducted primarily in the UK, USA, Taiwan, China, and France. The study samples ranged from 406 to 1,712,821, and the follow-up durations ranged from 2.3 to 12 years. 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.The quality of studies was good, ranging from 6 to 8 points.

We used Egger's (P = 0.41) and Begg's (P = 1.00) tests to test the publication bias, and there was no statistical evidence of publication bias among the studies. We performed a sensitivity analysis by changing the analysis model from a random-effects model to a fixed-effects model, and found that the results were unstable for different analysis models, giving different

results. When using the random-effects model, we found that gout or hyperuricemia did not increase the risk of dementia, with a pooled hazard ratio of 0.94 (95% CI, 0.69, 1.28). Using the fixed-effects model, we found that gout or hyperuricemia increased the risk of dementia, with a pooled hazard ratio of 1.07 (95% CI, 1.04, 1.10). In consideration of the high heterogeneity of the included articles, we preferred the results given by the random-effects model.

In our meta-analysis, we found no increased risk of dementia among patients with gout or hyperuricemia, with a pooled hazard ratio of 0.94 (95% CI, 0.69, 1.28), with an I^2 of 98%, $P < 0.001$(Figure 2). However, there was a decreased risk of AD in patients with gout or hyperuricemia, with a pooled hazard ratio of 0.78 (95% CI, 0.64, 0.95), with an I^2 of 55%, $P = 0.01$ (Figure 3).

Lu et al. and Latourte et al. analyzed dementia patients in European, Singh et al. analyzed patients in North America, and Hong et al. investigated data of Asian populations. Lu et al. used AD diagnostic codes, which were positively predicted at 83% in a UK-based GPRD-based validation study. Singh et al. and Hong et al. used ICD9-CM as the diagnostic criterion for dementia. Latourte et al. used the DSM-IV criteria for the diagnosis of dementia and NINCDS-ADRDA as the diagnostic standard for AD. We consider that the reasons for the high degree of heterogeneity are related to the differences between races, diets, climate factors, clinical characteristics between different countries, lack of standardized design, inclusion criteria, and uniform follow-up time, which may affect the final results universality.

DISCUSSION

This meta-analysis was based on four articles of cohort studies performed in different

countries, thus providing a comprehensive evaluation of the association between dementia and gout or hyperuricemia. The four cohort studies analyzed 121,136 cases of dementia, of which Lu et al. included only patients with AD, while the other three analyzed data on all types of dementia. In addition, of the four articles included in our meta-analysis, only one described a lower risk of developing vascular dementia (VD) in patients with gout.[10] All studies were assessed as being of high quality based on the Newcastle–Ottawa Scale. The included studies had adjustments for other risk factors. Our meta-analysis showed no statistically significant risk of dementia in patients with gout or hyperuricemia compared with the non-gout or non-hyperuricemia controls. In contrast, gout or hyperuricemia was negatively correlated with the risk of AD. The existing reports hold different views on the pathophysiological mechanism of the relationship between gout and dementia. Whether a high uric acid level has predisposes to or protects against dementia has not been uniformly summarized. Several studies have indicated that inflammatory pathways may play an important role in increasing the risk of dementia.[15] [16] Hyperuricemia causes persistent systemic inflammation of gout and can also affect the inflammatory capacity of immune cells.[17] However, there has been no unified conclusion about the relationship between dementia and gout or hyperuricemia, which prompted our meta-analysis.

To date, it has been controversial whether gout or hyperuricemia and dementia are related. There have been several speculations about the mechanism by which gout could affect the onset of dementia. Some reports propose that gout or hyperuricemia may increase the risk of dementia[9] [14] because chronic inflammation from gout has some effects on the brain. Some studies have suggested that high inflammatory cytokine levels in brains with

neurodegeneration play important roles in the pathogenesis of dementia.[18-20] Others have suggested that gout is associated with oxidative stress, which may play a key role in the pathogenesis of dementia.[21 22] Elevated inflammatory cytokines can damage endothelial cells, activate inflammatory cells, and cause oxidative stress, which promotes the progression of atherosclerosis.[19 23] Atherosclerotic cardiovascular diseases are well-established risk factors for dementia.[24] Additionally, there has been some evidence that an association of hyperuricemia with cardiovascular disease is due to concomitant oxidative stress.[25] Taken together, chronic inflammation and oxidative stress may be the final pathways in dementia and gout or hyperuricemia, which may explain the high risk of dementia reported by some studies in elderly people with gout or hyperuricemia.

In contrast, some studies have confirmed that gout or hyperuricemia may decrease the risk of dementia.[8 10] Uric acid has been proposed to have both a pro-oxidant effect[26] and an anti-oxidant effect.[27 28] It can have some pro-oxidant effects in its oxidized state, but there is relatively little evidence that this is an important mechanism for circulating uric acid, in comparison to its antioxidant role. Uric acid is well established as an important circulating antioxidant and free-radical scavenger. It is an antioxidant and metal chelator in vitro.[29 30] It can effectively clear peroxynitrite and hydroxyl radicals[27 31 32] and reduce oxidative stress as an antioxidant, may exert possible neuroprotective effects. Moreover, it has been reported that the pathogenesis of AD is related to mitochondrial dysfunction. Some studies have shown that uric acid might preserve mitochondrial function and suppress oxyradical accumulation;[27] thereby inhibiting the cytotoxic activity of lactoperoxidase[33] and repairing free radical-induced DNA damage.[34] Scheepers et al. reported that lower level of serum urate may

lead to a higher risk of dementia since antioxidant capacity might be reduced with the decreasing of the urate concentration among middle-aged women. They surveyed and followed up 1462 38 to 60 years old women over 44 years and found that a higher serum urate may have a protective effect on dementia including Alzheimer's disease and vascular dementia.[35] Euser et al. investigated that high serum urate levels are associated with a reduced risk of dementia and further improved cognitive function.[36] In recent study, Liu et al.'s study came to the same conclusion that lower level of uric acid is associated with AD in Chinese.[37] In our study, we analyzed the AD subgroup of dementia and found that gout can reduce the risk of AD. This may also confirm the neuroprotective role of uric acid. Unlike asymptomatic hyperuricemia, patients with gout receive anti-inflammatory or urate-lowering therapies, and it cannot be excluded that those drugs will affect the risk of dementia. Pandey et al. reported that a urate-lowering drug benzbromarone can antagonize oxidative stress and improve the function of vascular endothelial cells, which may be related to the reduced probability of dementia in patients with gout.[38] However, it is not yet fully clear whether anti-gout drugs can reduce the incidence of dementia and more researches will enable us to understand the effects of anti-gout drugs on dementia.

Our study found no correlation between dementia and gout or hyperuricemia. Dementia involves variable clinical symptoms, multiple subtypes, and complex pathogenesis, which may explain the contradictory results of studies on gout or hyperuricemia. More research is needed to support this viewpoint. The risk of AD is inversely proportional to gout, and the neuroprotective mechanism of uric acid may play a dominant role in the pathogenesis of AD.

However, there were some potential limitations to our study. First, there were only four studies in our meta-analysis, whose number of articles included were relatively small. Moreover, the cohort studies were mostly medical registry-based studies, which would raise concerns over coding inaccuracy and misclassification. Second, although studies included had been adjusted for other risk factors, the statistical heterogeneity is still high, which might be attributed to differences in demographics, dietary factors, environmental factors, and clinical characteristics in different countries, or lack of standardized design, inclusion criteria, and follow-up time. Third, this was a pooled analysis of observational studies, which could only demonstrate an association, but not causality. Therefore, we cannot determine the impact of gout, hyperuricemia, or other unknown confounding factors on the outcome of dementia risk. Moreover, in the sensitivity analysis, we found that the results were unstable when using different analysis models. Considering the high heterogeneity of the included articles, we preferred the results given by the random-effects model. Consequently, caution is needed when interpreting the present meta-analysis findings.

In conclusion, our meta-analysis of cohort studies suggested that there is no risk of dementia among patients with gout and hyperuricemia. However, high uric acid levels have a protective effect on AD. More investigations are needed to demonstrate the potential relationship between dementia and patients with gout and hyperuricemia.

Contributors Conceptualization: YL Methodology: S-YP and R-JC. Formal analysis: Z-JX; data curation: Q-PZ. Writing original draft preparation: S-YP and R-JC. Writing review and editing: YL. Approval of final manuscript: All authors

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Patient and public involvement No patient involved.

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Table 1 Characteristics of included studies in the meta-analysis.

	Lu N et al. [8]	Singh JA et al.[14]	Hong JY et al. [10]	Latourte A et al. [9]
Country	UK	USA	Taiwan, China	France
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Year	2016	2018	2015	2018
Age, mean years	65	75.2	63.5	72.9
Male, %	71	42.6	63	38.7
Diagnosis of gout or Hyperuricemia	diagnostic code using the Read classification	(ICD-9-CM) codes	(ICD9-CM) codes	Hyperuricemia: ≥360 μmol / L for men, ≥300 μmol / L for women.
Diagnosis of dementia	AD diagnostic codes	(ICD-9-CM) codes	(ICD9-CM) codes	DSM-IV NINCDS-ADRDA
Subtype of dementia	AD	All subtypes of dementia	All subtypes of dementia AD、VD	All subtypes of dementia AD
Number of dementia with controls	309/238805	106346/1416173	5905/114742 AD:102/114742 VD:210/114742	78/1192 AD:55/1192
Number of dementia with cases	1942/59224	5310/296648	1214/28769 AD:542/28769 VD:991/28769	32/406 AD:21/406
Adjusted confounders	Age, gender, entry-time, BMI, smoking, alcohol use, physician visits, social deprivation index, comorbidities, and medication use.	Age, gender, race, medical comorbidities, common medications for cardiac diseases, and gout.	Age, gender, relevant comorbidities.	Age, gender, tobacco and alcohol consumption, cholesterol, medical comorbidities, medication use

Follow-up years (mean or mean ± SD)	5	2.3 (1.7)	4.3(2.1)	12
Quality grading	7 points	6 points	7 points	8 pionts

(AD: Alzheimer's disease; VD: Vascular dementia; DSM-IV: Diagnostic and Statistical Manual of Mental disorders Version IV; NINCDS-ADRDA: the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; ICD9-CM: International Classification of Diseases Ninth Revision, Clinical Modification codes; BMI: body mass index)

Figure 1 Flow diagram showing the identification and selection of cohort studies included in the review.

Figure 2 Forest plot showing an association between dementia and patient's with gout and hyperuricemia.

Figure 3 Forest plot showing an association between AD and patient's with gout and hyperuricemia.

Figure 1 Flow diagram showing the identification and selection of cohort studies included in the review.

Figure 1

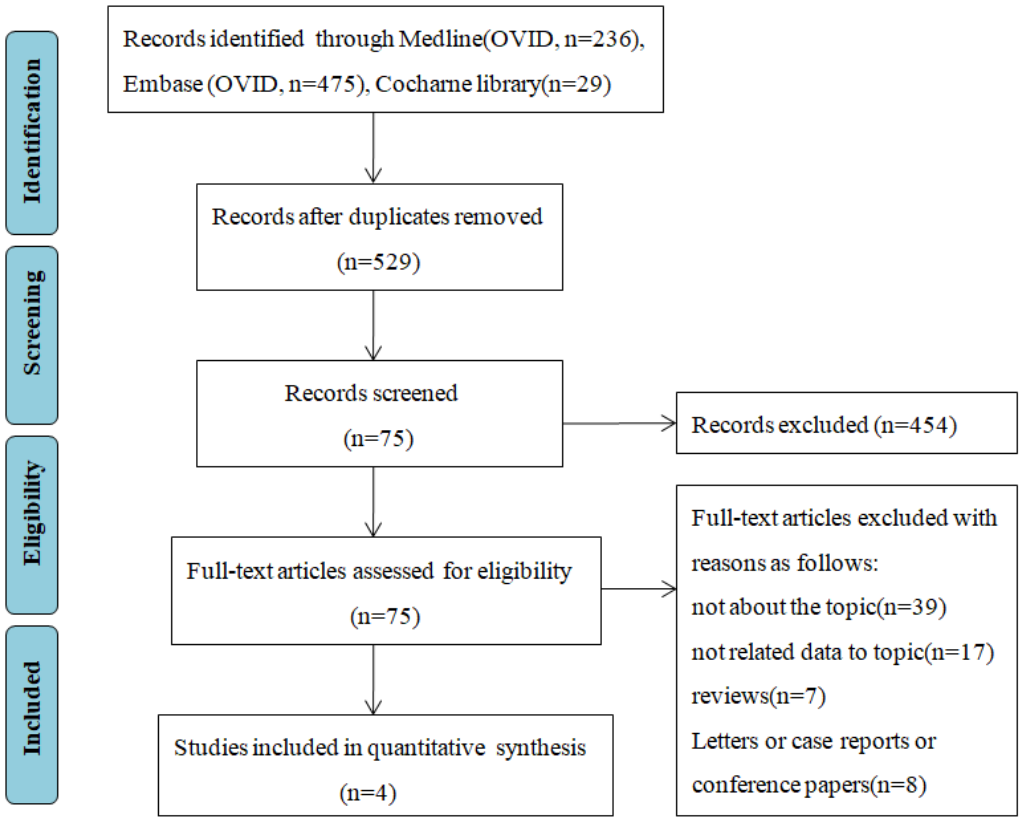


Figure 2 Forest plot showing an association between dementia and patient's with gout and hyperuricemia.

Figure 2

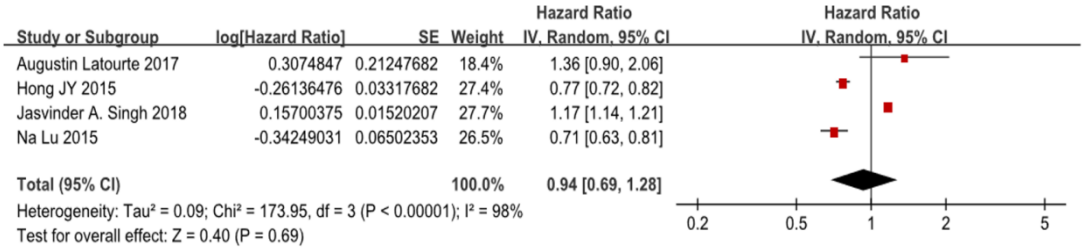
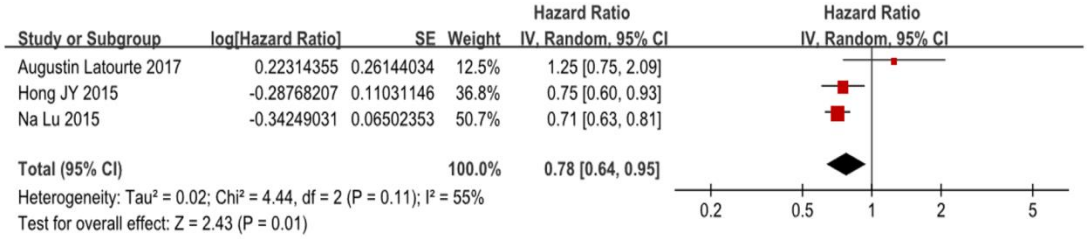


Figure 3 Forest plot showing an association between AD and patient's with gout and hyperuricemia.

Figure 3



Appendix 1

Medline Ovid Search Strategy

1. exp Dementia/

2. Delirium/

3. Wernicke Encephalopathy/

4. Delirium, Dementia, Amnestic, Cogni-tive Disorders/

5. dement*.mp.

6. alzheimer*.mp.

7. (lewy* adj2 bod*).mp.

8. deliri*.mp.

9. (chronic adj2 cerebrovascular).mp.

10. (organic brain disease or organicbrain syndrome).mp

11. (normal pressure hydrocephalus andshunt*).mp.

12. benign senescent forgetfulness.mp.

13. (cerebr* adj2 deteriorat*).mp.

14. (cerebral* adj2 insufficient*).mp.

15. (pick* adj2 disease).mp.

16. (creutzfeldt or jcd or cjd).mp.

17. huntington*.mp.

18. binswanger*.mp.

19. korsako*.mp.

20.1-19/OR

21.exp gout/

22.gout.mp.

23. exp hyperuricemia /

24. uric acid.mp.

25.20-23/OR

26. 20 and 25

Appendix 2

Embase search strategy

1.exp gout/

2.gout.mp.

3. exp hyperuricemia /

4. uric acid.mp.

5.1-4/OR

6. exp *dementia/

7. dement*.ti,ab.

8. alzheimer*.ti,ab.

9. (lewy* adj2 bod*).ti,ab.

10. (frontotemporal* or FTD or FTLD).ti,ab.

11.6-10/or

12. 5 and 11

Appendix 3

Cochrane librarysearch strategy

1.exp gout/

2.gout.mp.

3. exp hyperuricemia /

4. uric acid.mp.

5.1-4/OR

6. exp *dementia/

7. dement*.ti,ab.

8. alzheimer*.ti,ab.

9. (lewy* adj2 bod*).ti,ab.

10. (frontotemporal* or FTD or FTLD).ti,ab.

11.6-10/or

12. 5 and 11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	none
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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