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ORIGINAL ARTICLE

The relationship between uric acid and brain health from observational studies

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Abstract

This study conducts a systematic literature review and meta-analysis regarding the potential influence of serum uric acid levels on cerebral small vessel diseases and the cognitive status in the prodromal stages of dementia. We identified four different cerebral small vessel diseases and three specific domains of cognitive performance to be considered in the literature search. The analysis contained 14 studies (13 cross-sectional design and one longitudinal design) with 11,502 participants measuring the relationship between uric acid and cerebral small vessel disease. In both continuous and categorical analyses, significant associations were found between hyperuricemia and cerebral small vessel diseases (continuous data: pooled OR: 1.00, 95%CI: 1.00–1.01 and categorical data: pooled OR: 1.42, 95%CI: 1.15–1.75). For the relationship between uric acid and cognitive performance, 19 studies with 49,901 participants were considered, including eight cohort studies, and 11 cross-sectional studies. The cross-sectional data showed that a marginal relationship existed between uric acid and global cognition (β: 0.00, 95%CI: -0.01–0.00). The pooled analysis of cohort studies indicated that higher uric acid had a deleterious effect on attention and executive function (continuous data: β: -0.02, 95%CI: -0.04–0.00 and categorical data: β: -0.03, 95%CI: -0.07–0.00). Conclusion: Our study indicated that a higher level of uric acid had an adverse effect on brain health. Furthermore, a high level of uric acid is related to cognitive decline in attention and executive function, which may exist a long time before the diagnosis of dementia.

Keywords Uric acid · Cerebral small vessel disease · Cognitive impairment

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Introduction

Dementia has become a significant social burden in the current aging world, and the identification of associated risk factors to design effective preventive interventions is urgently needed (Brookmeyer et al. 2011). Cerebral small vessel diseases, such as white matter lesions, cerebral microbleeds, lacunar infarction, and brain atrophy, as well as some specific cognitive deterioration, have been reported as indicators of dementia (Debette and Markus 2010; Jack 2000). A growing number of studies have focused on the relationship between serum uric acid and changes to the brain and cognition (Kim et al. 2020; Jeong et al. 2017), which occur silently many years before the diagnosis of dementia.

Uric acid (UA), the end product of the metabolism of purine nucleotides, has been reported as a key factor of many dementia-related diseases, such as stroke (Bos et al. 2006), hypertension (Sundström et al. 2005), obesity (Zheng et al. 2017), lipid abnormalities (Ali et al. 2019), diabetes (Dehghan et al. 2008), and cerebrocardiovascular diseases

(Arora et al. 2018). Acting as a free radical scavenger (Dimitroula et al. 2008), UA is neuroprotective through reducing oxidative stress (Lam et al. 2016). However, UA-induced endothelial (Khosla et al. 2005) and inflammatory system dysfunction (Ruggiero et al. 2006; Prasad et al. 2017) may negatively impact brain function. Oxidative stress and vascular pathophysiology both contribute to dementia, and recent epidemiological studies have shown the controversial effects of elevated serum UA levels on cognitive impairment (Euser et al. 2009; Afsar et al. 2011).

A recent meta-analysis indicated a positive relationship between serum UA with dementia and cognitive impairment, especially of the vascular subtype (Khan et al. 2016); however, it focused only on global cognition change with cross-sectional data and the pooled evidence of serum UA and cerebral small vascular disease is absent. On this basis, the current analysis aims to improve our knowledge regarding the association between serum UA with cerebral small vessel disease and specific cognition functions.

Material and methods

Study inclusion

The PubMed, Embase, and Web of Science databases were searched for relevant studies published up to Dec 2021. Different kinds of cerebral small vessel diseases and specific cognitive performances were included. In the current analysis, we considered four cerebral small vessel diseases: brain atrophy, white matter lesions, cerebral microbleeds, and lacunar infarction, and three specific cognitive performances: global cognition, attention and executive function, and learning and memory. Further pertinent articles were supplemented by inspecting the references of the found articles. This report was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (Stroup et al. 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Knobloch et al. 2011).

Inclusion and exclusion criteria

Studies that met the following inclusion criteria were used in this review: (1) it is an original article published in English; (2) the article clearly defines UA, cerebral small vessel diseases, or specific cognitive statement; (3) the study diagnoses cerebral small vessel diseases based on magnetic resonance imaging (MRI) or measures a specific cognitive performance by generally agreed tests; (4) the study uses a physical diagnosis of serum UA; (5) the study provides quantitative measures of the association between UA with cerebral small vessel diseases and cognitive performance; and (6) the study uses cross-sectional, case–control, or cohort epidemiological study designs. Exclusion criteria were as follows: (1) the publication is a review, case report, animal study, or letter to the editor; (2) the publication does not clearly define clinical outcomes; (3) the author cannot provide valid data after being contacted; and (4) the study includes duplicated data.

For the current analysis, the relationships between UA and cerebral small vessel diseases were measured using odds ratio (OR) and 95% confidence interval (CI). The standardized effect estimate of β, accompanied with 95%CI, was selected for assessing the association between UA and the continuous cognitive tests score, while category data were performed using OR and 95%CI.

Data extraction and quality assessment

Two investigators (XYT, JBZ) independently extracted the data from the enrolled studies using identical methods, focusing on study quality, population characteristics, underlying diseases, as well as outcomes. The bias risk of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale criteria (NOS) (Stang 2010). Following the guidelines of NOS, we rated the quality of the studies by awarding stars in each domain. In case of disagreements, the investigators included the other authors in discussions to arrive at a consensus. The data used to support the findings of this study are available from the publicized articles directly.

Statistical analysis

Heterogeneity between studies was evaluated by the I^2 metric and the variance between studies by Tau^2. Random-effects models were conducted if $I^2 > 50\%$, and fixed-effects models were chosen if $I^2 \leq 50\%$. We obtained the data directly from the studies, and adjusted odds ratio (OR) were pooled as a measure of associations across all studies using categorical data. Continuous standardized cognitive test scores were pooled using effect estimate β with a 95%CI. We regarded all the effect estimates of standardized cognitive test scores as consistent and converted standard error into 95%CI.

To find more potential factors impacting the bias, we further conducted sub-group and sensitivity analyses. Sensitivity analyses were conducted to assess the influence of a single result on the pooled estimate. Egger's asymmetry test evaluated potential publication bias (Egger et al. 1997). P-values were two-tailed, and $P < 0.05$ was considered statistically significant. The statistical analyses were performed

with STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search outcomes and validity assessment

For the association between UA and cerebral small vessel disease, the search strategy identified 307 potentially relevant reports, of which 68 were excluded as they were duplicates. The remaining 239 manuscripts were subjected to title and abstract screening. A further 201 publications were removed, as they were reviews, letters, conference abstracts, or independent studies. Therefore, 38 articles were eligible for full-text review and data assessment. Finally, 24 articles were excluded for lack of relevant information (n = 21) or the absence of a full publication (n = 3). A total of 14 studies (Kim et al. 2020; Jeong et al. 2017; Sun et al. 2016; Suzuki et al. 2016; Heo and Lee 2010; Kikuchi et al. 2011; Li et al. 2016; Shih et al. 2012; Zhou et al. 2014; Schretlen et al. 2007a, b; Han et al. 2016; Ryu et al. 2013; Latourte et al. 2018a, b; Verhaaren et al. 2013) with a total of 11,502 participants met the inclusion criteria, of which 13 (Kim et al. 2020; Jeong et al. 2017; Sun et al. 2016; Suzuki et al. 2016; Heo and Lee 2010; Kikuchi et al. 2011; Li et al. 2016; Shih et al. 2012; Zhou et al. 2014; Schretlen et al. 2007a, b; Han et al. 2016; Ryu et al. 2013; Latourte et al. 2018a, b) provided cross-sectional data and one (Verhaaren et al. 2013) provided longitudinal data (Fig. 1A). Table 1 provides an overview of the 14 eligible studies.

The literature search outcome regarding the association between UA and cognitive performance resulted in 3052 reports. After excluding duplicates (n = 634), screening titles and abstracts, reviewing full texts, and assessing data, 19 studies with a total of 49,901 participants were selected, consisting of 8 cohort studies (Euser et al. 2009; Verhaaren et al. 2013; Alam et al. 2020; Puy et al. 2018; Wang et al. 2017; Beydoun et al. 2016; Molshatzki et al. 2015; Sleeman et al. 2019) and 11 cross-sectional studies (Afsar et al. 2011; Sun et al. 2020; Perna et al. 2016; Wu et al. 2013; Vannorsdall et al. 2014; Xue et al. 2017; Al-khateeb et al. 2015; Liu et al. 2017; Schretlen et al. 2007a, b; Baena et al. 2017; Kueider et al. 2017) (Fig. 1B). Table 2 provides the characteristics of these 11 studies.

One cross-sectional study focused on the mediated effect of cerebral small vessel disease on UA level and cognitive performance (Vannorsdall et al. 2008).

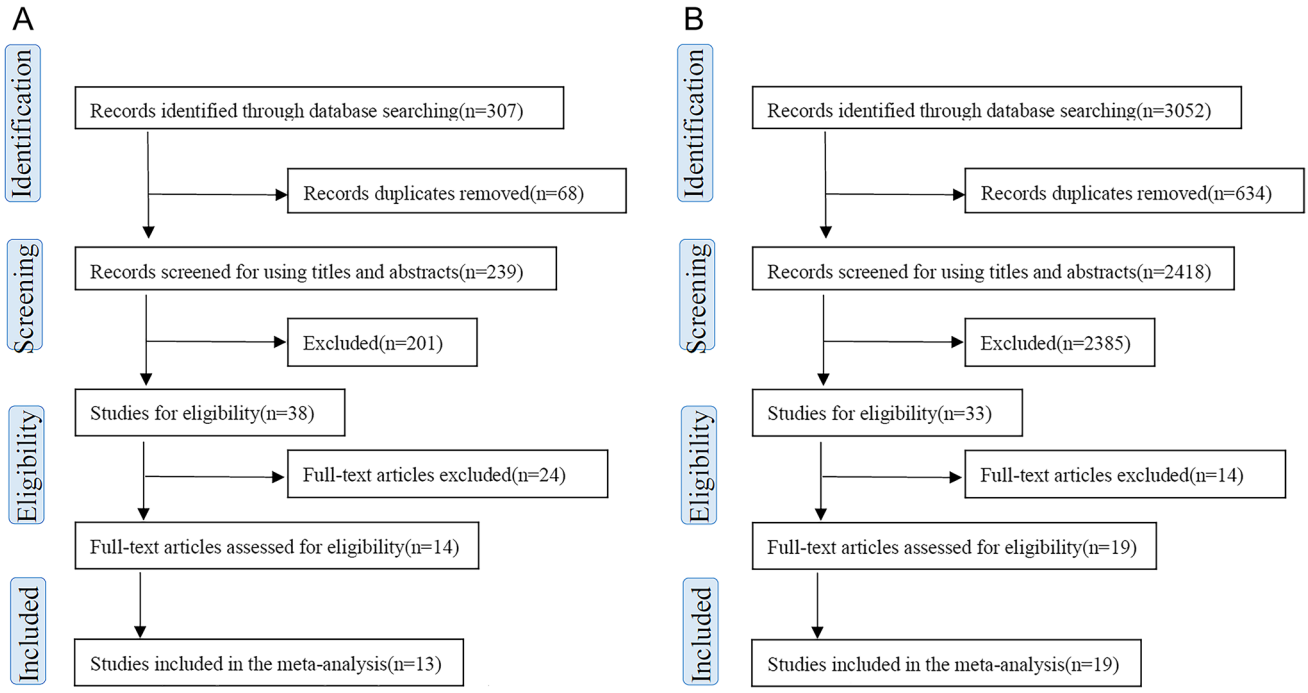

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of studies included. **A**. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of studies about the association between uric acid and cerebral small vessel diseases. **B**. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of studies about the association between uric acid and cognitive performance

Table 1 Characteristics of studies included about the association between serum uric acid and cerebral small vessel diseases

Study	Year	Sample	Age/mean (SD)	Study design	Female/%	Diabetes/%	Hypertension/%	BMI/mean (SD)	Smoking/%	Basic diseases	Main outcome
Verhaaren	2013	814	62.0 (5.4)	cohort: follow-up 5 years	50.90%	8.40%	/	26.8 (3.5)	17.60%	/	hyperuricemia is related to white matter atrophy
Schretlen	2007	177	60.4 (18.7)	cross-sectional	51.98%	13.50%	33.89%	27.2 (5.0)	23.72%	/	mildly elevated serum uric acid is associated with increased burden of cerebral ischemic pathology, particularly in older adults
Heo	2010	1577	53.7 (10.6)	cross-sectional	41.60%	11.90%	50.50%	/	49.30%	/	an increased level of uric acid may be a risk factor for the presence of silent brain infarction
Kikuchi	2011	50	59.5 (6.5)	cross-sectional	44%	43.50%	72.00%	22.1 (3.2)	30.50%	hemodialysis	the odds of silent brain infarction was increased with elevated uric acid
Shih	2012	231	72.5 (5.4)	cross-sectional	53.20%	13.00%	84.40%	23.8 (2.8)	3.00%	/	hyperuricemia was positively associated with high grade deep white matter hyperintensities in older men, but not in women
Ryu	2013	724	67.4 (8.9)	cross-sectional	64.20%	34.12%	68.25%	24.0 (3.1)	27.60%	acute ischemic stroke	serum uric acid is independently associated with the presence of cerebral microbleeds
Zhou	2014	1098	67.6 (8.5)	cross-sectional	54.30%	18.30%	55.70%	23.0 (2.5)	16.70%	/	serum uric acid levels positively correlated to leukoaraiosis severity
Han	2016	130	64.7 (9.95)	cross-sectional	20.80%	31.50%	54.60%	24.3 (3.06)	33.10%	acute lacunar infarction	serum uric acid was associated with cerebral white matter hyperintensities in patients with acute lacunar infarction
Li	2016	1280	18–85	cross-sectional	31.40%	5.78%	21.25%	/	/	/	blood uric acid level was correlated with the risk of acute cerebral infarction

Table 1 (continued)

Study	Year	Sample	Age/mean (SD)	Study design	Female/%	Diabetes/%	Hypertension/%	BMI/mean (SD)	Smoking/%	Basic diseases	Main outcome
Sun	2016	480	63.59 (9.10)	cross-sectional	59.79%	26.04%	35.83%	/	13.96%	/	elevated serum uric acid level was independently associated with greater odds of higher severity of periventricular white matter lesions, particularly in women
Suzuki	2016	228	64.3 (10.1)	cross-sectional	53.90%	/	/	23.2 (3.1)	36.40%	/	none of these analyses could prove any significant association between serum uric acid levels and the presence of white matter lesions
Jeong	2017	2686	56.5 (8.2)	cross-sectional	47.80%	13.20%	36.20%	24.1 (3.0)	17.50%	/	high serum uric acid value was associated with higher prevalence of cerebral microbleeds in male, but lower prevalence of cerebral microbleeds in female subjects
Latourte	2018	1598	72.4 (4.1)	cross-sectional	61.70%	7.60%	75.70%	25.4 (3.8)	5.80%	/	did not find any association between serum uric acid levels and magnetic resonance imaging markers of cerebrovascular disease
Kim	2020	429	70.6 (8.0)	cross-sectional	55.90%	/	/	24.0 (3.1)	4.90%	/	there is an association of low serum uric acid with Alzheimer's disease-related cerebral hypometabolism

SD Standard deviation

Table 2 Characteristics of studies included about the association between serum uric acid and cognitive performance

Study	Year	Sample	Age/mean (SD)	Study design	Female/%	Diabetes/%	Hypertension/%	BMI/mean (SD)	Smoking/%	Basic disease	Main outcome
Euser	2009	1724	69.4 (8.6)	cohort: follow up 11.1 years	61%	11%	/	/	65%	/	higher levels of uric acid are associated with better cognitive function later in life
Verhaaren	2013	814	62.0 (5.4)	cohort: follow up 5 years	50.90%	8.40%	/	26.8 (3.5)	17.60%	/	hyperuricemia is related to worse cognition
Molshatzki	2015	446	62.3 (6.4)	cohort: follow up 9.8 years	0	18.16%	/	26.7	/	pre-existing cardiovascular disease	low uric acid levels in patients with pre-existing cardiovascular disease are associated with poorer cognitive function a decade later
Beydoun	2016	2630	47.0 (0.3)	cohort: follow up 4.64 years	53.95%	/	/	19.7 (0.3)	43.70%	/	a higher serum uric acid was associated with faster cognitive decline over-time in a visual memory/ visuo-construction ability test
Wang	2017	12,798	59.3 (9.7)	cohort: follow up 1.33–2.42 years	53.50%	5.60%	24.20%	/	29.20%	/	higher baseline uric acid level was associated with better cognition in later life but not with rates of cognitive decline
Puy	2018	40	62.58 (11.01)	cohort: follow up 344 days	45%	41.00%	84.60%	27.5 (5.92)	43.80%	chronic kidney disease	cognitive impairment was independently associated with high serum uric acid levels
Sleeman	2019	154	66.4 (10.4)	cohort: follow up 54 months	35.10%	7.80%	31.20%	/	5.80%	Parkinson's disease	lower serum urate concentration is not associated with global cognition
Alam	2020	11,169	56.7 (5.7)	cohort: follow up 24.1 years	58.76%	13.36%	14.57%	/	58.32%	/	higher levels of mid-life serum uric acid were associated with faster cognitive decline

Table 2 (continued)

Study	Year	Sample	Age/mean (SD)	Study design	Female/%	Diabetes/%	Hypertension/%	BMI/mean (SD)	Smoking/%	Basic disease	Main outcome
Schretlen	2007	96	73.1 (7.7)	cross-sectional	50.00%	14.60%	46.60%	26.7 (4.4)	19.35%	/	even mild elevations of uric acid might increase the risk of cognitive decline among older adults
Afsar	2011	247	60.5 (11.0)	cross-sectional	52.20%	43.70%	62.80%	29.0 (4.6)	26.70%	chronic kidney disease	serum uric acid levels are inversely associated with mild cognitive dysfunction in subjects with chronic kidney disease
Wu	2013	2006	60.6 (7.0)	cross-sectional	57.40%	21.50%	33.93%	25.2 (3.7)	26.83%	/	uric acid might play a protective role in aging-associated decline in cognitive function
Vannorsdal	2014	436	73.9 (2.8)	cross-sectional	52.20%	13.30%	33.90%	27.2 (5.1)	24.40%	/	higher baseline serum uric acid was associated with poorer working memory
AI-Khateeb	2015	40	71.50 (9.11)	cross-sectional	37.50%	/	/	/	45%	/	no significant correlation between Mini-Mental State Examination and serum uric acid
Perna	2016	1144	73.9 (2.8)	cross-sectional	57.30%	22.30%	61.00%	/	6.80%	/	serum uric acid showed an inverse association with cognitive function among women
Baene	2017	12,215	50.0 (7.5)	cross-sectional	55.30%	16.80%	24.30%	26.9 (4.3)	13.20%	/	serum uric acid was significantly associated with better cognitive performance on an executive function test in middle-aged men, but not in women

Table 2 (continued)

Study	Year	Sample	Age/mean (SD)	Study design	Female/%	Diabetes/%	Hypertension/%	BMI/mean (SD)	Smoking/%	Basic disease	Main outcome
Kueider	2017	1451	64.2 (14.0)	cross-sectional	49.80%	/	/	/	/	/	higher serum uric acid levels at baseline were associated with attenuated declines in attention and visuospatial abilities in men
Liu	2017	2102	71.2 (6.6)	cross-sectional	59.70%	/	/	25.0 (3.4)	11.00%	/	higher serum uric acid levels were positively associated with cognitive function among Chinese community elderly
Xue	2017	115	68.3 (5.2)	cross-sectional	39.10%	19.10%	27.80%	22.9 (3.1)	27.80%	/	a low uric acid level is a risk factor for mild cognitive impairment
Sun	2020	274	69.2 (11.5)	cross-sectional	38.00%	28.10%	72.60%	/	31.80%	ischemic stroke	serum uric acid level was correlated with post stroke cognitive impairment

SD Standard deviation

Quality assessment

The NOS evaluation tool was used for assessing the quality of all studies enrolled, including those aimed at measuring the association between UA and cerebral small vessel diseases or cognitive performance. The quality assessment results were at a scale of 6 to 9, indicating high qualities (Supplemental Tables 1 and 2).

The association between UA and cerebral small vessel diseases

Thirteen cross-sectional studies (Kim et al. 2020; Jeong et al. 2017; Sun et al. 2016; Suzuki et al. 2016; Heo and Lee 2010; Kikuchi et al. 2011; Li et al. 2016; Shih et al. 2012; Zhou et al. 2014; Schretlen et al. 2007a, b; Han et al. 2016; Ryu et al. 2013; Latourte et al. 2018a, b) of 10,688 subjects focused on the association between serum UA level with cerebral small vessel disease, including white matter lesions, lacunar infarct, and cerebral microbleeds. In five studies (Kim et al. 2020; Jeong et al. 2017; Sun et al. 2016; Kikuchi et al. 2011; Li et al. 2016) with 4925 subjects, using UA as a continuous variable, a significant association was found between UA and cerebral small vessel diseases (pooled OR: 1.00, 95%CI: 1.00–1.01). Further sub-group analyses showed statistically significant results only between UA and white matter lesions (OR: 1.00, 95%CI: 1.00–1.00). No relationship existed between UA and lacunar infarctions (OR: 1.25, 95%CI: 0.72–2.16) or cerebral microbleeds (OR: 0.99, 95%CI: 0.57–1.72) (Fig. 2A). When the analysis was limited to those without the basic disease, the significant relationship between continuous UA level and cerebral small vessel disease remained (pooled OR: 1.00, 95%CI: 1.00–1.00). Only one study (Jeong et al. 2017) provided data regarding different genders respectively, which showed that per 1 mg/dl increase of UA the risk of cerebral microbleeds could increase by 1.29 times (95%CI: 1.06–1.57) among men, but has no effect on women (OR: 0.73, 95%CI: 0.52–1.02). Sensitivity analyses showed that the combined OR was consistent at every point when omitting any one study.

Among eight studies (Suzuki et al. 2016; Heo and Lee 2010; Shih et al. 2012; Zhou et al. 2014; Schretlen et al. 2007a, b; Han et al. 2016; Ryu et al. 2013; Latourte et al. 2018a, b) with 5763 participants, using UA as a categorical variable, the results indicated that higher levels of UA were related to cerebral small vessel diseases (pooled OR: 1.42, 95%CI: 1.15–1.75), compared with the lower dose ranges of UA. Further sub-group analyses showed similar results as those obtained with continuous data. Significant associations existed only between UA and white matter lesions (OR: 1.47, 95%CI: 1.02–2.11), however, higher levels of UA had no effect on lacunar infarction (OR: 1.14, 95%CI: 0.74–1.74) or cerebral microbleeds (OR: 1.34, 95%CI:

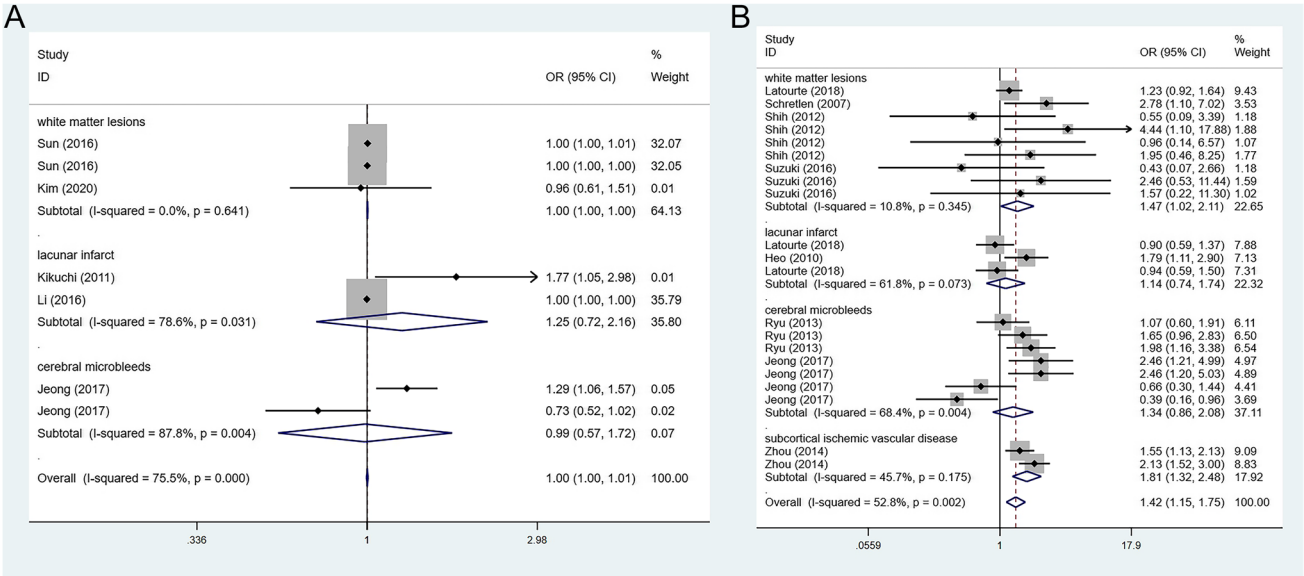

Fig. 2 The association between uric acid and cerebral small vessel diseases among cross-sectional studies. **A**. The association between continuous uric acid and cerebral small vessel diseases among cross-sectional studies. **B**. The association between categorical uric acid and cerebral small vessel diseases among cross-sectional studies. **Abbreviation:** OR, odds ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random-effects estimate of sub-group analysis studies. Weights are from the random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study

0.86–2.08) (Fig. 2B). A comparison of the highest range of UA with the lowest possible range that impacts cerebral microbleeds showed a significant result with the pooled OR of 1.38 (95%CI: 1.03–1.85). Among people without basic disease, we found similar results regarding higher UA levels and cerebral small vessel diseases (pooled OR: 1.39, 95%CI: 1.09–1.78), as in those older than 60 years (pooled OR: 1.43, 95%CI: 1.16–1.76). Three studies (Jeong et al. 2017; Heo and Lee 2010; Shih et al. 2012) provided data regarding different genders, and the pooled results showed that high UA was a risk factor of cerebral small vessel diseases in men (OR: 2.08, 95%CI: 1.49–2.90), but not in women (OR: 0.83, 95%CI: 0.49–1.41). When omitting studies one by one, sensitivity analyses showed consistent results.

Only one cohort study (Verhaaren et al. 2013) with 814 participants focused on the association between serum UA level and brain atrophy. During a mean follow-up of five years, Verhaaren et al. found that higher UA levels were associated with total brain volume, particularly regarding white matter volume (difference in Z-score of white matter volume per standard deviation increase in UA: -0.07, 95%CI: -0.12 – -0.01).

The association between UA and cognitive performance

Across 11 cross-sectional studies (Afsar et al. 2011; Sun et al. 2020; Perna et al. 2016; Wu et al. 2013; Vannorsdall et al. 2014; Xue et al. 2017; Al-khateeb et al. 2015; Liu et al. 2017; Schretlen et al. 2007a, b; Baena et al. 2017; Kueider et al. 2017) with 20,126 participants, the current analysis focused on the relationship between UA and specific cognitive performances using continuous data. Ten studies(Afsar et al. 2011; Sun et al. 2020; Perna et al. 2016; Wu et al. 2013; Vannorsdall et al. 2014; Xue et al. 2017; Al-khateeb et al. 2015; Liu et al. 2017; Baena et al. 2017; Kueider et al. 2017) that provided related data were enrolled in this analysis. We identified three specific cognitive performances: global cognition, attention and executive function, and learning and memory. The pooled β was 0.00 (95%CI: -0.01–0.00) for the association between UA and whole cognitive performance. Further sub-group analyses indicated a significant correlation between continuous UA level and lower learning and memory performance (β: -0.05, 95%CI: -0.10–0.00) (Fig. 3A). Next, we limited our analysis to participants older than 60 years and found that UA was related with worse cognitive performance (β: 0.00, 95%CI: -0.00–0.00), similar to those without basic diseases (β: -0.01, 95%CI: -0.01–0.00). Three studies (Liu et al. 2017; Baena et al. 2017; Kueider et al. 2017) included data regarding different genders; no significant relationship existed between continuous UA and any cognitive performance in men (global cognition: β: 0.01, 95%CI: -0.04–0.05; attention and executive function: β: 0.00, 95%CI: -0.01–0.02; learning and memory: β: -0.02, 95%CI: -0.07– 0.02). In women, continuous UA was correlated with worse performance in attention and executive function (β: 0.00, 95%CI: -0.01–0.00), but not learning and memory (β: -0.07, 95%CI: -0.19–0.06), nor

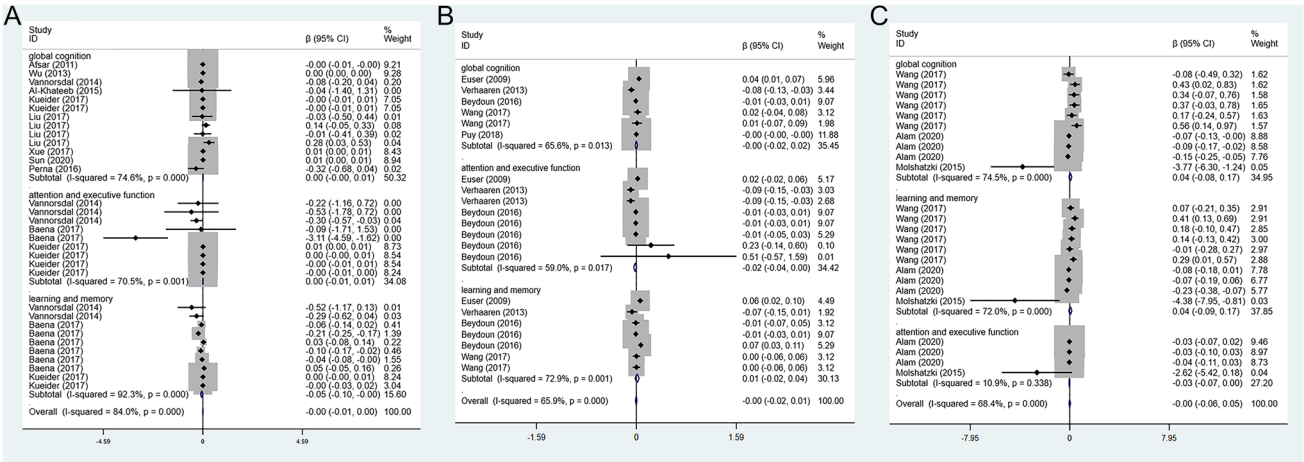

Fig. 3 The association between uric acid and cognitive performance. **A**. The association between continuous uric acid and cognitive performance among cross-sectional studies. **B**. The association between continuous uric acid and cognitive performance among cohort studies. **C**. The association between categorical uric acid and cognitive performance among cohort studies. **Abbreviation:** CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random-effects estimate of sub-group analysis studies. Weights are from the random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study

global cognition (β: 0.07, 95%CI: -0.12–0.26). When omitting studies one by one, sensitivity analyses showed consistent results.

There were eight cohort studies (Euser et al. 2009; Verhaaren et al. 2013; Alam et al. 2020; Puy et al. 2018; Wang et al. 2017; Beydoun et al. 2016; Molshatzki et al. 2015; Sleeman et al. 2019), containing 29,775 participants, included in this analysis. A total of six studies (Euser et al. 2009; Verhaaren et al. 2013; Puy et al. 2018; Wang et al. 2017; Beydoun et al. 2016; Sleeman et al. 2019) regarded UA level as a continuous variable and found that no significant relationship existed between UA and pooled cognitive performance (β: 0.00, 95%CI: -0.02–0.01). Sub-group analyses showed that UA had a negative effect on attention and executive function (β: -0.02, 95%CI: -0.04–0.00) but no effect on global cognition (β: 0.00, 95%CI: -0.02–0.02) and learning and memory (β: 0.01, 95%CI: -0.02–0.04) (Fig. 3B). The results regarding the relationship between continuous UA and cognitive performance remained non-significant after limiting to analyses among individuals without basic disease (β: 0.00, 95%CI: -0.02–0.01), older than 60 years (β: -0.02, 95%CI: -0.05–0.01), or with a follow-up longer than three years (β: -0.01, 95%CI: -0.03–0.01). Sensitivity analyses showed consistent results after omitting studies one by one.

Three studies (Alam et al. 2020; Wang et al. 2017; Molshatzki et al. 2015) used UA level as categorical data. When setting the lowest UA level range as the reference group, higher levels of UA did not affect the cognitive performance (β: 0.00, 95%CI: -0.06–0.05). However, sub-group analyses showed a significant negative link of higher UA levels with attention and executive function (β: -0.03, 95%CI: -0.07–0.00) (Fig. 3C). Due to the small sample, a further sensitivity analysis was omitted.

Only one cohort study (Wang et al. 2017) had conducted an analysis of the relationship between UA and cognitive performance in different genders; the analysis contained 12,798 participants and found that a higher UA level had no effect on the rates of cognitive decline both in males and females.

Publication bias

According to the Cochrane Handbook version 5.1.0 (Higgins et al. 2019), tests for funnel plot asymmetry should be used only when there are enough studies included in the analysis. In this study, the *P*-value of the Egger test was 0.840 for the relationship between UA and cerebral small vessel disease. For the relationship between UA and cognitive performance, *P*-values were 0.358 and 0.052 for the cohort and cross-sectional studies, respectively. All *P*-values were > 0.05 and indicated no significant bias among them. The funnel figures of these studies showed an asymmetrical inverted distribution, which is consistent with the results of the Egger test (Supplemental Fig. 1).

White matter lesions as the link between serum UA levels and cognitive decline

One cross-sectional article (Vannorsdall et al. 2008) assessing individual differences in how white matter hyperintensities volume mediates the association between UA and mild cognitive dysfunction, was included. The study found that after adding white matter hyperintensities volume to the model, the relationship between UA and the cognitive performance of working memory, processing speed, and ideational fluency became significant ($P < 0.01$). The results indicated that white matter lesions could play a role in mediating the relationship between serum AU levels and cognitive impairment. No longitudinal evidence existed to confirm this hypothesis.

Discussion

The present meta-analysis consisted of 14 studies regarding the association of UA and cerebral small vessel disease, 19 studies on the association of UA and cognitive performance, and one study regarding the mediated effect of cerebral small vessel disease on the deleterious effect of AU on cognitive performance. Our results showed that: (1) higher serum UA was linked with cerebral small vessel disease, especially white matter lesions, and the phenomenon was more prevalent in males than in females; (2) higher serum UA impaired attention and executive functions, but not global cognition; and (3) white matter lesions may mediate the effect of UA on cognitive performance, however, more longitudinal evidence is needed.

Comparison with other studies

Consistent with our current analysis, a recent meta-analysis has found no association between serum UA levels and the Mini-Mental State Examination (MMSE) test scores ($r = 0.08$, $p = 0.27$), a symbol of global cognition (Khan et al. 2016). However, many studies have declared UA as a neuroprotective factor of brain health, especially regarding Alzheimer's Disease (Du et al. 2016), and some others indicated a U-shaped association between serum UA and cognitive function (Huang et al. 2019). These studies have focused on diagnosed dementia or whole cognitive dysfunction and not the condition before obvious clinical symptoms or specific cognitive performance. The present study contains both cross-sectional and longitudinal designed studies and identifies

a harmful effect of hyperuricemia on brain health, starting at an early stage, therefore enriching the available previous findings.

Potential mechanisms

The potential mechanisms of UA impacting on brain health remain unclear. Serum AU levels are regulated by dietary purine intake, xantine oxidase activity, and renal UA excretion (Tana et al. 2018). Several studies have reported UA as an antioxidant (Sautin and Johnson 2008), while some authors have also suggested that UA has pro-oxidant effects (Sautin et al. 2007). Thus, the extent of this effect is uncertain due to this complex interrelationship. It has been suggested that elevated serum UA levels are associated with an increased inflammatory response to oxidative stress (Maxwell and Bruinsma 2001), which can be an important link between high serum UA levels and cognitive impairment (Satizabal et al. 2012). Moreover, UA impairs endothelial function and induces vascular damage by reducing nitric oxide bioavailability (Zhao et al. 2009; Sánchez-Lozada et al. 2008). The differences found in males and females may be explained by sex hormones, which can suppress the activity and expression of enzymes related to vascular reactive oxygen species (Miller et al. 2007). Additionally, females were found to achieve better oxidative balance than males by enhancing mitochondrial respiratory chain function and antioxidant activities (Guevara et al. 2009). Finally, some genetic abnormalities of the purine metabolism may be an explanation of the close association between serum UA and cognitive decline (Sebesta and Stiburkova 2014; Latourte et al. 2018a, b).

Public health impact

In recent years, the prevalence of hyperuricemia and asymptomatic hyperuricemia has been increasing (Liu et al. 2015; Benn et al. 2018). Today, more than 47 million individuals worldwide are affected by dementia (Livingston et al. 2017), and this prevalence is expected to increase in the current aging society (Freedman et al. 2018). The current analysis indicates that hyperuricemia is a risk factor of cerebral small vessel disease and declined cognitive performance, which are regarded as "pre-clinical" symptoms of dementia, especially in males. Thus, controlling UA levels should be considered in the dementia-prevention management of subjects with hyperuricemia. Because hyperuricemia is also exhibited as a risk factor of cardiovascular disease (Liu et al. 2012; Johnson et al. 2018), therefore increasing the mortality of dementia, the public health care systems should pay more attention to the early monitoring of serum UA levels.

Strengths and limitations of the study

To the best of our knowledge, we have conducted the first meta-analysis and systemic review to measure the effect of UA on cerebral small vessel disease and cognitive performance. The strengths of our study include the adjustment for multiple covariates, including sex, age, education, smoking, body mass index, basic diseases, and medication use. Furthermore, we explicitly defined our inclusion criteria, developed a comprehensive search strategy, considered all types of study designs, performed a duplicate quality assessment of enrolled studies, extracted the available data and transformed them uniformly, and cautiously analyzed all factors.

Regarding the study's limitations, the most significant include: 1) Due to the absence of data, we could not conduct a pooled analysis of the association between UA and cerebral small vessel disease in cohort studies, as well as the role of white matter lesions in the association between UA levels and cognitive impairment. Further longitudinal evidence on this topic is needed. 2) Some studies thought the effect of UA on brain health varied between genders because of different cut-off levels (Jeong et al. 2017; Baena et al. 2017). Several studies provided data regarding genders and the results had low credibility due to the small amount of data. A more comprehensive reliable analysis was not possible because of the different effect estimates used in the analyses. 3) Some UA-lowering drugs, including allopurinol and febuxostat, may affect brain health (Singh and Cleveland 2018), which was not considered in the current analysis due to the lack of information. 4) The heterogeneity of results may be due to differences in ethnicity of the study populations and methods of UA measurement; few articles provided the necessary data, therefore, it was difficult to analyze the heterogeneity further.

Conclusions

According to our results, high UA serum levels have a deleterious effect on brain health, including cerebral small vessel disease and cognitive performance. However, these results need further validation and replication through longitudinal studies, especially regarding the potential mediated effect of cerebral small vessel disease on UA related cognitive impairment.

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Author contribution Xingyao Tang and Jian-Bo Zhou designed the subject and plan of this study; Zhi-Hui Song, and Marly Augusto Cardoso participated in data analysis, and drafting the manuscript. Rafael Simó revised this manuscript. All authors whose names emerge on the submission approved the version to be published.

Data availability All data used in the current analysis were obtained directly from the published studies.

Declarations

Conflicts of interest The authors declare that they do not have conflict of interest.

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