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ORIGINAL ARTICLE

Uric acid levels and their association with vascular dementia and Parkinson's disease dementia: a meta-analysis

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Abstract

Objectives To explore the association between uric acid (UA) levels and vascular dementia (VaD) and Parkinson's disease dementia (PDD), a meta-analysis was conducted.

Methods The relevant studies were identified by searching PubMed, Embase, Web of Science, and Cochrane Collaboration Database up to May 2022. Pooled analysis, sensitivity analysis, and publication bias examination were all conducted. All analyses were performed by using STATA 16.

Results Twelve studies with a total of 2097 subjects were included. The pooled analysis showed that UA levels were not associated with VaD (WMD = - 10.99 μmol/L, 95% CI (- 48.05, 26.07), $P = 0.561$) but were associated with PDD (WMD = - 25.22 μmol/L, 95% CI (- 43.47, - 6.97), $P = 0.007$). The statistical stability and reliability were evaluated using sensitivity analysis and publication bias outcomes.

Conclusion UA levels are associated with PDD but not with VaD. This study will help to strengthen our knowledge of the pathophysiologies of VaD and PDD, and promote the development of prevention and treatment strategies.

Keywords Uric acid levels · Vascular dementia · Parkinson's disease dementia · Meta-analysis

Introduction

Dementia is characterized as a syndrome rather than a particular disease that can seriously affect an individual's work and life [1]. Because of its high prevalence, dementia has become a serious public health issue around the world [2]. Vascular dementia (VaD) and Parkinson's disease dementia (PDD) are both common types of dementia [3]. For a long time, factors related to VaD and PDD have attracted worldwide attention.

Previous studies have reported that dementia is influenced by many factors, including age, gender, educational level, obesity, and disease history [4–6]. Some researchers have demonstrated that neuronal injury can be caused by oxidative damage which might affect the pathophysiology of dementia [7–9]. Our previous study reported that low antioxidant capacity might be related to VaD, and treatment with antioxidants might mitigate cognitive impairment [10]. Similar results were also obtained in PDD [11].

As the most abundant endogenous antioxidant in blood, uric acid (UA) has been considered to exert neuroprotective effects by removing ROS and nitrite [12, 13]. However, studies have shown that high levels of UA can promote inflammation and oxidation in special environments and may cause neuronal injury [14, 15]. Many researchers have paid close attention to whether UA levels are associated with VaD and PDD, and several studies have been conducted. Nevertheless, no consistent conclusion has been reached on whether UA levels are related to VaD or PDD. Therefore, a meta-analysis was conducted in the study to investigate the association.

Methods

The study was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

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Search strategy

The PubMed, Embase, Web of Science, and Cochrane Collaboration Database were searched for all relevant citations up to May 2022. The following terms were used for searching: (uric acid OR UA OR urate OR hyperuricemia) AND (vascular dementia OR VaD OR Parkinson's disease dementia OR PDD OR dementia). No language or other restrictions were applied to the search strategy. References of the retrieved studies were also screened to identify available articles.

Inclusion and exclusion criteria

Criteria for study inclusion were based on the following: (1) the association between UA levels and VaD and/or PDD was

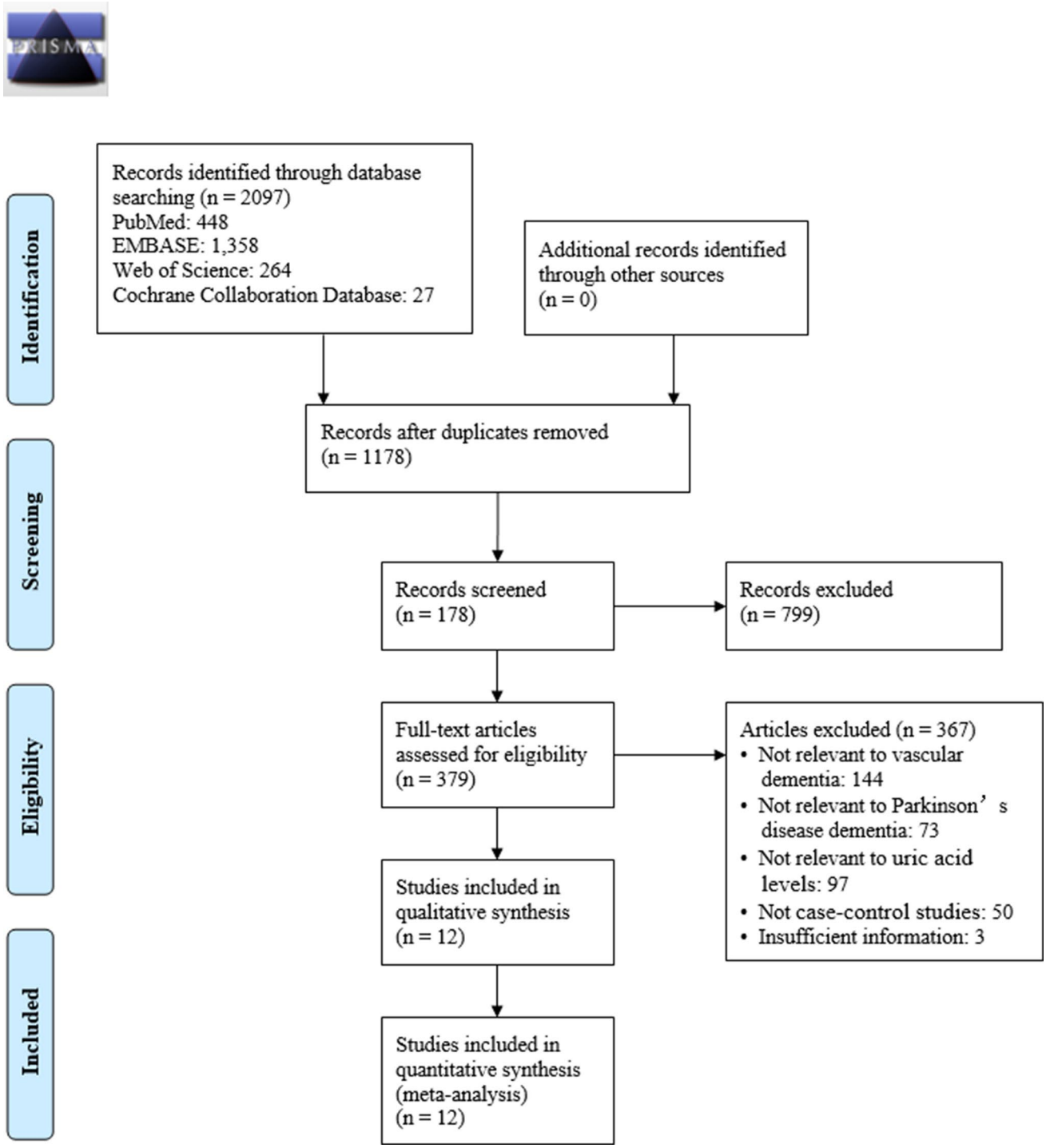


Fig. 1 Flow diagram of study selection

Table 1 Characteristics of the included studies

First author, published year	Country	Continent	Mean age (yr)	Male percentage (%)	Sample		Uric acid (μmol/L)		Dementia types	NOS score
					Case	Control	Case	Control		
Serdarevic N, 2020 [21]	Bosnia and Herzegovina	Europe	71.7	100.0	100	100	321.3 ± 85.8	263.0 ± 62.5	VaD	7
Liu HX, 2020 [22]	China	Asia	65.6	70.5	111	79	360.0 ± 110.0	348.0 ± 86.0	VaD	6
Tuven B, 2017 [23]	Turkey	Europe	NA	NA	16	1119	376.0 ± 181.5	343.9 ± 108.3	VaD	6
			NA	NA	15	1119	277.3 ± 111.9	343.9 ± 108.3	PDD	
Xu Y, 2016 [24]	China	Asia	67.7	53.8	127	81	300.1 ± 110.5	336.6 ± 103.6	VaD	8
Hatanaka H, 2015 [25]	Japan	Asia	82.8	47.5	27	53	323.1 ± 74.4	338.6 ± 100.0	VaD	7
Cervellati C, 2014 [26]	Italy	Europe	78.6	38.2	54	48	363.2 ± 94.8	317.0 ± 118.5	VaD	7
González-Aramburu I, 2014 [27]	Spain	Europe	64.2	57.0	72	271	299.9 ± 101.2	318.3 ± 83.3	PDD	8
Maetzler W, 2011 [28]	Germany	Europe	62.7	61.5	20	76	285.6 ± 83.3	303.5 ± 54.5	PDD	7
Polidori MC, 2004 [29]	Italy	Europe	76.4	35.9	23	55	193.6 ± 46.6	312.9 ± 82.3	VaD	8
Foy CJ, 1999 [30]	UK	Europe	75.9	53.7	37	58	266.7 ± 92.4†	300.0 ± 106.4†	VaD	6
			74.5	55.3	18	58	268.9 ± 80.4†	300.0 ± 106.4†	PDD	
Tohgi H, 1993 [31]	Japan	Asia	68.5	NA	15	14	283.0 ± 91.0	303.0 ± 70.0	VaD	7
Maesaka JK, 1993 [32]	America	North America	77.9	NA	6	11	330.0 ± 20.0	350.0 ± 30.0	VaD	7

NA, not available; *NOS*, Newcastle-Ottawa quality assessment scale; *VaD*, vascular dementia; *PDD*, Parkinson's disease dementia

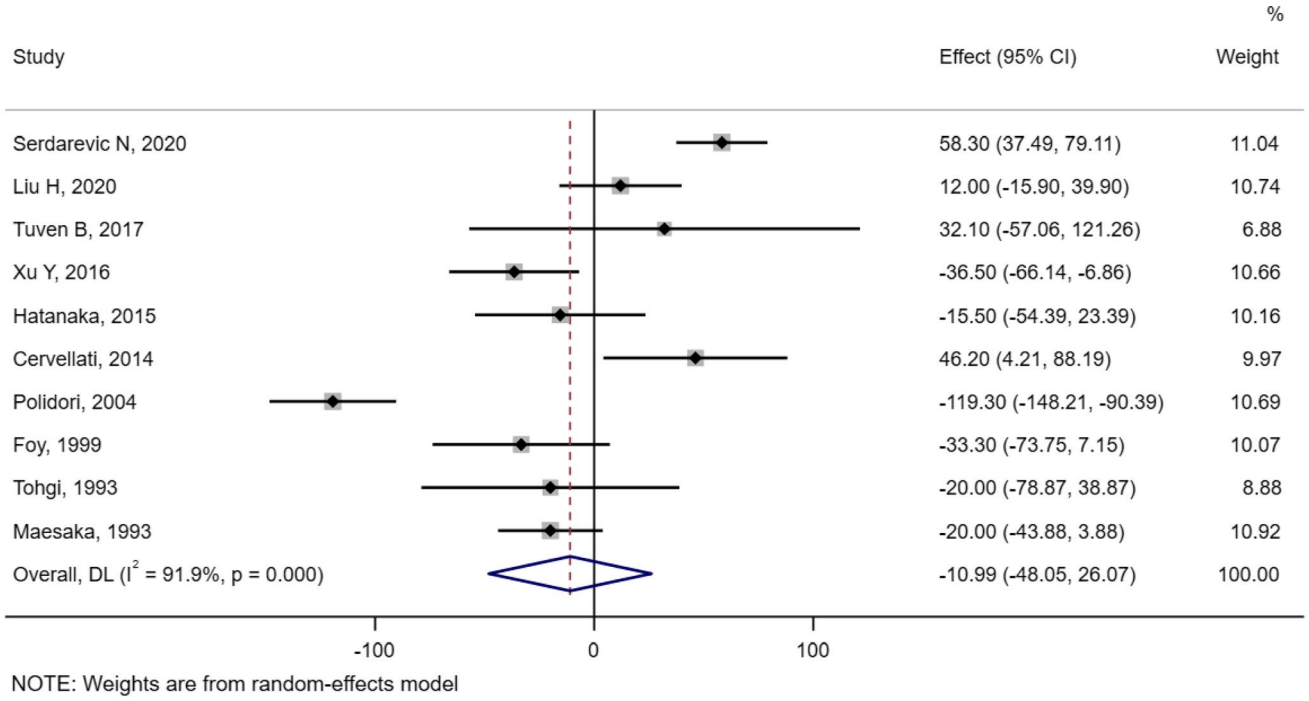
†Mean ± standard deviation estimated by median (interquartile range)

involved; (2) it should be a case-control study; (3) subjects in the case group were VaD or PDD patients, while the control group was not; and (4) the study should provide mean and standard deviation (SD) values of UA for each group. When only the median and interquartile ranges were provided, the mean and SD were estimated according to the formula [16].

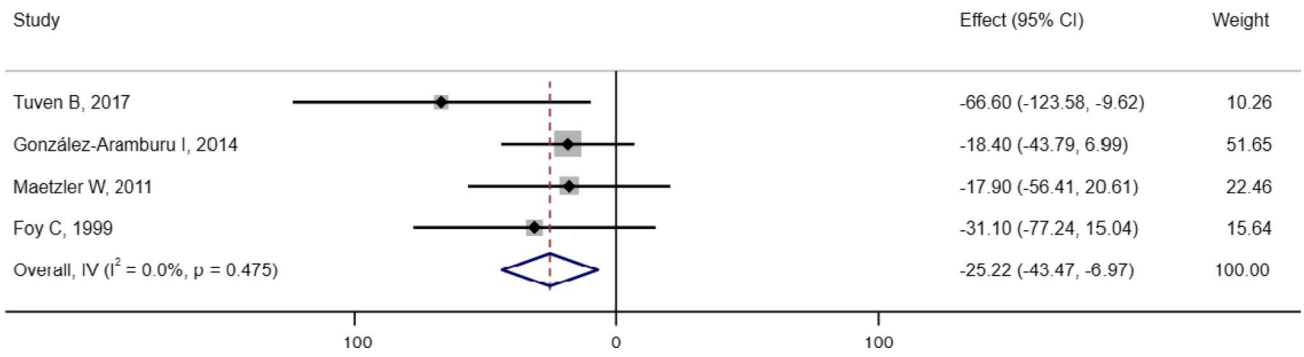
Studies were excluded according to the following criteria: (1) reviews, case reports or letters; (2) animal or cell studies; and (3) repeated publication of data from the same population.

Data extraction

All data were recorded for further evaluation separately by two reviewers, and any discrepancy was resolved by the third investigator. The following baseline data were collected: first author's name, year of publication, country, mean age, male percentage, number of patients in the case and control groups, and mean and SD values of UA in each group. Corresponding author was contacted for studies with inadequate information.



(a) Vascular dementia



(b) Parkinson's disease dementia

Fig. 2 Forest plot of weighted mean difference of vascular dementia and Parkinson's disease dementia associated with uric acid levels

Quality assessment

The Newcastle-Ottawa quality assessment scale (NOS) [17], a nine-star system, was used to assess the quality of the included studies. This scale evaluates studies according to selection, comparability and exposure. A study awarded a score ≥ 6 was considered high quality.

Statistical analysis

Weighted mean difference (WMD) and 95% confidence interval (CI) were utilized to evaluate correlation strength between UA levels and VaD/PDD. Statistical heterogeneity was identified by Q statistic and I^2 statistic. A random-effect model was applied when heterogeneity was defined as substantial (Q statistic $P < 0.05$ or $I^2 \geq 50\%$); otherwise, a fixed-effect model was applied [18]. Subgroup analyses were performed according to continent (Asian, European or North American), male percentage (≥ 50% or < 50%) and sample size (≥ 200 or < 200) to detect sources of heterogeneity. The sensitivity analysis was performed by sequentially removing studies. Begg's test and Egger's test were applied to identify publication bias [19, 20]. Stata 16 (Stata Corporation, College Station, TX, USA) was utilized to conduct the analyses.

Results

Studies and data included in the meta-analysis

A flow chart of search strategy is displayed in Fig. 1. After screening the 2097 retrieved candidate articles, 12 studies were included [21–32]. Detailed information on the included studies is summarized in Table 1. The included studies were published from 1993 to 2020, with sample sizes ranging from 17 to 1135. Seven studies were from Europe, four were from Asia, and one was from North America. According to the quality evaluation, the research design is reasonable and the outcome is clear. No study was excluded from the meta-analysis for reasons of quality.

Pooled and subgroup analyses

There were 10 studies concerning the relationship between UA levels and VaD in the meta-analysis. Overall, UA levels were not associated with VaD (WMD = - 10.99 μmol/L, 95% CI (- 48.05, 26.07), $P = 0.561$) (Fig. 2(a)). Substantial heterogeneity was discovered among the included studies ($I^2 = 91.9\%$, $P < 0.001$).

Subgroup analysis was conducted for the correlation between UA levels and VaD. In the subgroup analysis, studies were classified by continent, male percentage and sample size. However, there was no significant discrepancy among the subgroups (Table 2).

There were 4 studies concerning the association between UA levels and PDD in the meta-analysis. Overall, UA levels were associated with PDD (WMD = - 25.22 μmol/L, 95% CI (- 43.47, - 6.97), $P = 0.007$). (Fig. 2(b)). No statistical heterogeneity was discovered among the included studies ($I^2 = 0.0\%$, $P = 0.475$).

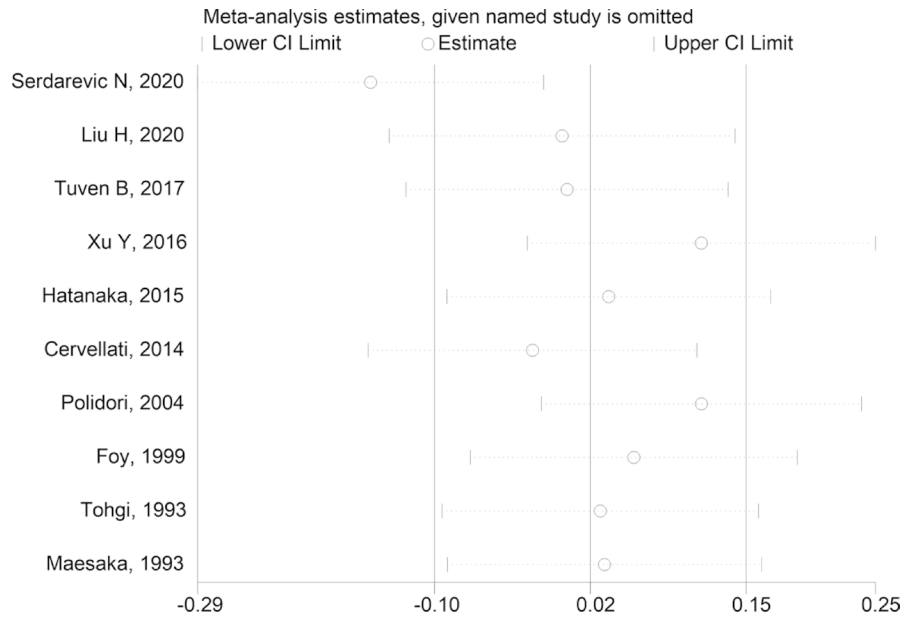
Sensitivity analysis

The sensitivity analysis was performed by sequentially removing studies to assess the effect of a unitary study on the pooled WMD. Statistical analysis indicated that the results were stable and reliable (Fig. 3).

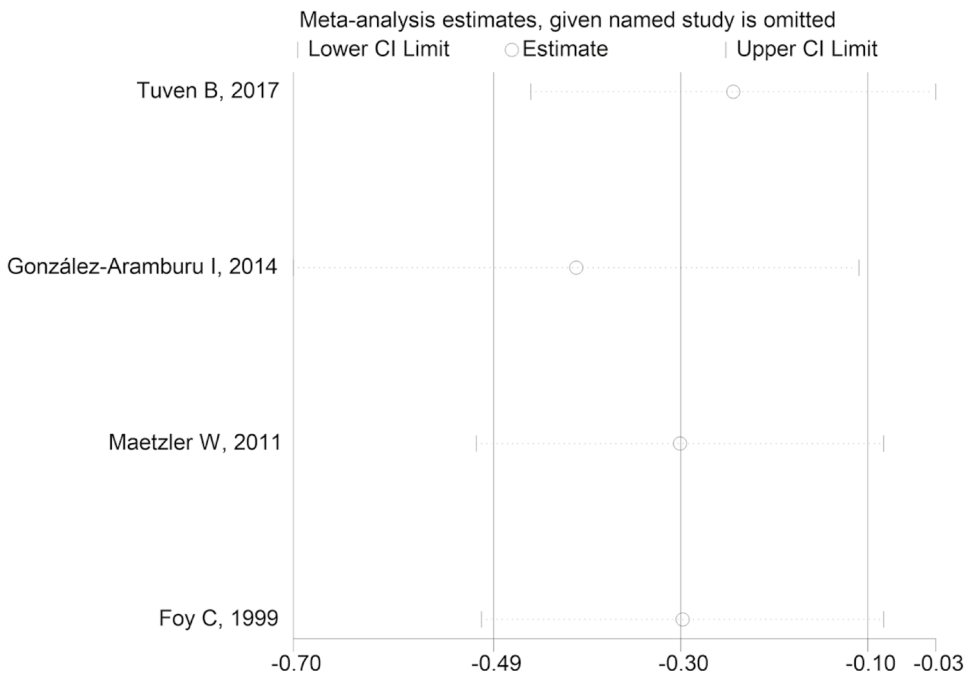
Table 2 The results of subgroup analysis

Subgroup	No. of study	WMD (μmol/L)	95% CI (μmol/L)		Heterogeneity	
			Lower	Upper	P	I^2 (%)
Continent						
Europe	5	- 4.54	- 85.56	76.48	< 0.001	96.1
Asia	4	- 13.64	- 38.31	11.02	0.135	46.1
North America	1	- 20.00	- 43.88	3.88	NA	NA
Male percentage						
≥ 50%	4	1.55	- 46.30	49.40	< 0.001	91.1
< 50%	3	- 30.43	- 130.04	69.18	< 0.001	95.6
Sample size						
≥ 200	3	16.76	- 57.82	91.33	< 0.001	92.4
< 200	7	- 22.14	- 62.95	18.67	< 0.001	89.9

WMD, weighted mean difference; *NA*, not available



(a) Vascular dementia



(b) Parkinson's disease dementia

Fig. 3 Sensitivity analysis of weighted mean difference between vascular dementia and Parkinson's disease dementia with uric acid levels

Publication bias

No evidence of obvious publication bias existed in the meta-analysis according to Begg's correlation (VaD: $P = 1.000$; PDD: $P = 0.089$) and Egger's regression (VaD: $P = 0.697$; PDD: $P = 0.182$). Additionally, no obvious asymmetry was shown in the shapes of funnel plots.

Discussion

Some studies have shown that oxidative damage might be related to dementia, including VaD and PDD. They have demonstrated that when neurons are exposed to oxidative damage factors (such as hypoxia, inflammatory factors, and aging), a large number of reactive oxygen species (ROS) will be produced. Excessive ROS can lead to oxidative damage, mainly manifested in protein denaturation, DNA breakage, and lipid peroxidation, resulting in neuronal death, which is closely related to the pathophysiologies of VaD and PDD [33, 34].

As a powerful antioxidant, UA has been supposed to alleviate neuronal damage via neuroprotective effects [35, 36]. However, evidence has also shown that high levels of UA are related to hypertension and metabolic syndrome, which might cause dementia by synergistically aggravating arteriosclerosis [37, 38]. Some evidence suggests that as an indicator of redox homeostasis, UA can relieve degenerative cascades in neurodegenerative diseases (such as dementia) [39, 40]. Furthermore, one study showed that exogenous UA might protect neurons from excitotoxic injury and play a neuroprotective role [41].

Ten independent studies were included in the current study, comprising 516 VaD patients and 1618 controls. The pooled analysis revealed that UA levels were not associated with the risk of VaD. We deduced that the antioxidant effect of UA might counteract its role in promoting arteriosclerosis. The pooled analysis showed that UA levels were associated with PDD, which was consistent with the findings of Huang et al. [42].

There are several limitations in this present study. First, the sample size was still relatively small in the meta-analysis, especially in exploring the association between UA and PDD. Second, although subgroup analysis and sensitivity analysis were conducted to explore the association between UA and VaD, the source of heterogeneity was not identified. Third, since only patients who visited the hospital were included in the study, some selection bias might affect the reliability of our findings. Despite the limitations, the statistical power was markedly improved based on substantial data from different studies. The statistical stability and reliability were further confirmed by sensitivity analysis and publication bias outcomes.

In summary, the meta-analysis shows that UA levels are associated with PDD but not with VaD. The study will help to strengthen the understanding of the pathophysiologies of VaD and PDD, and promote the development of prevention and treatment strategies. To obtain a clearer conclusion, more large sample size studies are needed.

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Author contribution Qian Li wrote the first draft, searched the literature, and extracted the data. Kaiwen Cen and Ying Cui searched the literature and extracted the data. Xu Feng conducted the data analysis. Xiaowen Hou designed the study and revised the manuscript.

Data availability All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

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