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Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis

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Abstract Serum uric acid (sUA) level may be associated with cognitive impairment/dementia. It is possible this relationship varies with dementia subtype, particularly between vascular dementias (VaD) and Alzheimer's (AD) or Parkinson's disease (PDD)-related dementia. We aimed to present a synthesis of all published data on sUA and relationship with dementia/cognition through systematic review and meta-analysis. We included studies that assessed the association between sUA and any measure of cognitive function or a clinical diagnosis of dementia. We pre-defined subgroup analyses for patients with AD, VaD, PDD, mild cognitive impairment (MCI), and mixed or undifferentiated. We assessed risk of bias/generalizability, and where data allowed, we performed meta-analysis to describe pooled measures of association across studies. From 4811 titles, 46 papers ($n = 16{,}688$ participants) met our selection criteria. Compared to controls, sUA was lower in dementia (SDM −0.33 (95%CI)). There were differences in association by dementia type with apparent association for AD (SDM −0.33 (95%CI)) and PDD (SDM −0.67 (95%CI)) but not in cases of mixed dementia (SDM 0.19 (95%CI)) or VaD (SDM −0.05 (95%CI)). There was no correlation between scores on Mini-Mental State Examination and sUA level (summary r 0.08, $p = 0.27$), except in patients with PDD (r 0.16, $p = 0.003$). Our conclusions are limited by clinical heterogeneity and risk of bias in studies. Accepting this caveat, the relationship between sUA and dementia/cognitive impairment is not consistent across all dementia groups and in particular may differ in patients with VaD compared to other dementia subtypes.

Keywords Uric acid · Dementia · Cognition · Systematic review · Meta-analysis

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Introduction

Despite increasing absolute numbers with dementia/cognitive impairment, our understanding of the

syndrome is limited and we have few therapeutic options. Identification of modifiable risk factors is critical, as this will allow for better understanding of pathophysiology, risk stratification, and potential interventions. Serum uric acid (sUA) has been suggested as a risk marker and possible therapeutic target for a number of common chronic diseases, particularly cardiovascular diseases (Dawson and Walters 2006).

The association of sUA and dementia is less clear. There are several published studies, but results have been equivocal or conflicting. The syndrome of dementia comprises a variety of distinct pathologies, and this may explain the mixed results from studies of sUA. As sUA has strong hydrophilic antioxidant properties, potential neuroprotective properties have been suggested that could be important in neurodegenerative diseases, such as Alzheimer's disease dementia (ADD) or dementias associated with Parkinson's disease (PDD). (Yu et al. 1998) The association of sUA with accelerated vascular disease could contribute to cognitive decline through clinical and occult cerebrovascular disease (Vanorsdall et al. 2008). The association between sUA and cognitive impairment/dementia may therefore differ between dementia subtypes. We sought to test this hypothesis through systematic review and meta-analysis to collate all available evidence on sUA and the relationship with dementia/cognitive impairment. Our aims were to describe association between sUA and a diagnosis of dementia and with measures of cognitive function.

Methods

Our study followed the conduct and reporting guidance as described in meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al. 2000) and the PROGRESS group guidance on prognosis based research. (Hemingway et al. 2013) We created a search protocol made available on an open access website (PROSPERO register, registration number CRD42014014898).

Eligibility All studies that reported sUA level in relation to a measure of cognitive function or in relation to a dementia diagnosis in human participants were potentially eligible with no restrictions based on language or year. We did not prespecify a preferred study methodology but formulated an analysis plan that studies would either be as follows:

1. Case control studies where sUA level was compared in patients with and without cognitive dysfunction;
2. Prospective studies of the relationship between incident dementia or cognitive decline and sUA; and
3. Cross-sectional studies of the relationship between sUA level and measures of cognitive function.

We did not limit the measures of cognitive function to any particular test or specify the method of sUA measurement. We excluded conference proceedings, theses, and case studies. Where the same data was presented in more than one publication, we used the primary (first) publication.

Search strategy: our search was conducted between November 2012 and July 2014 All aspects of study selection, extraction, and assessment were performed by two reviewers working independently (AK, JD) with recourse to a third arbitrator if required. Chinese language studies were reviewed by YF. We reviewed multiple international and cross-disciplinary electronic databases: EMBASE (OvidSP), CINAHL (EBSCO), MEDLINE (OvidSP), LILACS (Bireme), and ALOIS (Cochrane Dementia and Cognitive improvement Group) and included Chinese language medical databases (Chinese National Knowledge Infrastructure (CNKI) database, VIP and Wanfang databases). We used a concepts-based approach for creation of search terms; concepts of interest were around sUA and cognition/dementia (full search strategy in Supplementary information).

We reviewed all study titles from database searches. Abstracts of potentially relevant titles were assessed and full text of potentially eligible studies reviewed. We used forward and backward citation searching of relevant papers and repeated the process until no new titles were generated. As a test of validity of the search strategy, a researcher not involved in the original searches identified five exemplar papers that should be included in the analysis. We assessed if our search strategy identified all of these titles.

Data extraction and assessment For those studies not published in English language, translation services

were employed, or in the case of Chinese papers, they were translated by one of the authors (YF). We independently extracted data using a specific data extraction form (Supplementary materials).

We categorized diagnoses using the following labels: AD, MCI, mixed or undifferentiated, PDD, VaD. We used the diagnostic classification described in the primary paper. Under our rubric of VaD, we included vascular cognitive impairment and post-stroke cognitive impairment. Under our rubric of PDD, we included those diseases with a predominantly parkinsonian phenotype.

We assessed generalizability (external validity) and risk of bias of each study using a pre-specified, bespoke tool based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance (von Elm et al. 2008), Cochrane tools (Higgin et al. 2011), and the Newcastle-Ottawa scales (Wells GA) for cohort and case control studies (Supplementary materials).

Quantitative analysis We attempted meta-analysis where there were three or more eligible studies. For case-control data, we calculated pooled mean differences for sUA (standardized difference in means (SDM) and associated 95 % confidence interval (95 %)) or the odds of dementia according to sUA. For papers describing correlation of sUA and a cognitive test score (e.g., Folstein's Mini-Mental State Examination (Folstein et al. 1975 Nov)), we described summary correlation coefficient.

We assessed heterogeneity with visual inspection of forest plots and with the I^2 statistic, taking a value of >50 % to define substantial heterogeneity. In cases of substantial heterogeneity, we used random effects models.

We assessed publication bias using Egger's plots (funnel plots) for analyses where more than five papers were included. We used a one-tailed p value of <0.1 for Egger's regression intercept for quantitative assessment of potential publication bias.

All analyses were performed using Comprehensive Meta-analysis software (version 3.0 CMA group New Jersey USA). Given the large numbers of included papers and their heterogeneity, we present results grouped by study methodology and within this, by dementia type.

Results

Our search strategy identified 4811 titles. Of these, 69 papers were selected for full text review and 46 were eligible for inclusion. These 46 papers included 16,688 participants (Fig. 1). Five studies were written in Chinese (Wei et al. 2012; Qin and Yang 2009; Shang et al. 2009; Wang et al. 2009; You and Liu 2012), one in Japanese (Matsubayashi et al. 1988), and one in Turkish (Cankurtaran et al. 2013). Four authors were contacted for additional data and three responded. Our internal validity checks confirmed rigor of our search strategy, with all five exemplar papers included in the first search. Twenty-two studies were judged to be low risk of bias (eTable 1). The main sources of bias were performance bias and lack of adjustment for potential confounders.

Twenty-two papers included patients with AD ($n = 1194$, Table 1) (Ahlskog et al. 1995; Baldieras et al. 2008; Bowman et al. 2010; Can et al. 2013; Cankurtaran et al. 2013; Cascalheira et al. 2009; Cervelatti et al. 2013; Foy et al. 1999; Gackowski et al. 2008; Irizarry et al. 2009; Iuliano et al. 2010; Kasa et al. 1989; Kim et al. 2006; Maesaka et al.

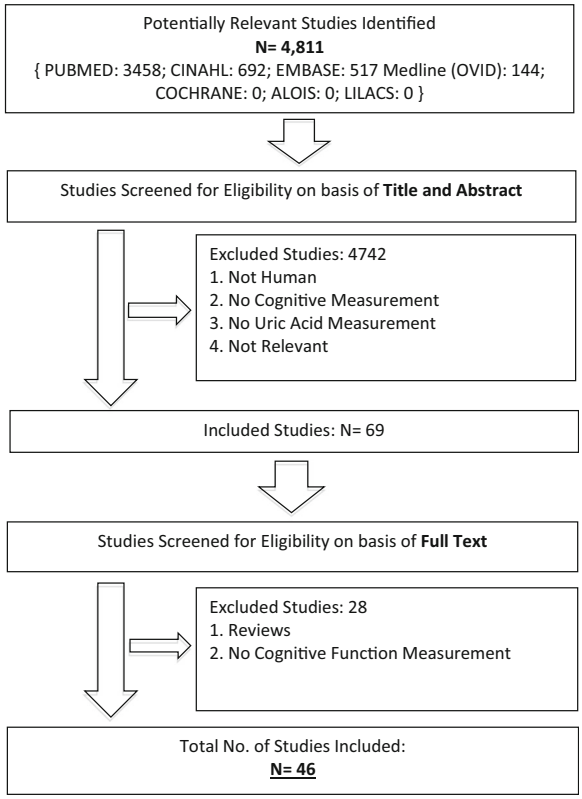

Fig. 1 PRISMA diagram

1993; Polidori and Meococci 2002; Polidori et al. 2004; Pulido et al. 2005; Rinaldi et al. 2003; Shang et al. 2009; Tohgi et al. 1993; Wikkelso et al. 1981; Zafrilla et al. 2006); 12 included patients with PDD (Afsar et al. 2011; Ahlskog et al. 1995; Annanmaki et al. 2011; Annanmaki et al. 2008; Ascherio et al. 2009; Foy et al. 1999; González-Aramburu et al. 2014; Maetzler et al. 2011; Moccia et al. 2014; Pan et al. 2013; Wang et al. 2009; You and Liu 2012) ($n = 1404$, Table 2); and 5 included patients with VaD (Foy et al. 1999; Maesaka et al. 1993; Matsubayashi et al. 1988; Tohgi et al. 1993; Wikkelso et al. 1981) ($n = 121$, Table 1).

Five studies (Cankurtaran et al. 2013; Cascalheira et al. 2009; Cicero et al. 2014; Li et al. 2010; Ruggiero Cherubini et al. 2009) ($n = 3281$ (489 with cognitive impairment/dementia + 2792 without)) described the relationship between sUA and incident dementia or cognition decline over time.

Case-control data

Thirty-two studies (Ahlskog et al. 1995; Annanmaki et al. 2011; Baldieras et al. 2008; Can et al. 2013; Cankurtaran et al. 2013; Cascalheira et al. 2009; Cervelatti et al. 2013; Cicero et al. 2014; Foy et al. 1999; Gackowski et al. 2008; González-Aramburu et al. 2014; Iuliano et al. 2010; Kasa et al. 1989; Kim et al. 2006; Li et al. 2010; Wei et al. 2012; Maesaka et al. 1993; Maetzler et al. 2011; Matsubayashi et al. 1988; Polidori and Meococci 2002; Polidori et al. 2004; Pulido et al. 2005; Qin and Yang 2009; Rinaldi et al. 2003; Ruggiero Cherubini et al. 2009; Shang et al. 2009; Tohgi et al. 1993; Wang et al. 2009; Wen et al. 2012; You and Liu 2012; Zafrilla et al. 2006) ($n = 7021$ participants) included a comparison of sUA between cases of cognitive impairment/dementia ($n = 2681$) and non-dementia controls (eTable 2). Five studies (Cankurtaran et al. 2013; Cascalheira et al. 2009; Cicero et al. 2014; Li et al. 2010; Ruggiero Cherubini et al. 2009) reported odds of dementia according to sUA; the remainder compared absolute measures of sUA between groups (eTable 3). There was substantial statistical heterogeneity in most analyses. There was a suggestion of possible publication bias (eFigure 1, $p = 0.04$ on Egger's regression intercept) across all studies, but not evident in analyses restricted to dementia subgroups (eFigures 2 to 4).

All cause dementia/cognitive impairment Across 31 studies, sUA was lower in cases of dementia compared to non-dementia controls with SDM −0.33 (95 %CI, $p < 0.001$) (Fig. 2). The summary odds of dementia on adjusted logistic regression analysis across five studies suggested no association with increasing sUA, OR 1.18 (95 % CI 0.96 to 1.46, $p = 0.12$) (eFigure 6).

AD There was variation in the reported association with 14 studies describing sUA as lower in cases; (Baldieras et al. 2008; Can et al. 2013; Cankurtaran et al. 2013; Gackowski et al. 2008; Kasa et al. 1989; Kim et al. 2006; Maesaka et al. 1993; Maetzler et al. 2011; Polidori and Meococci 2002; Polidori et al. 2004; Rinaldi et al. 2003; Shang et al. 2009; Tohgi et al. 1993; Zafrilla et al. 2006) 3 studies reported the converse (Cascalheira et al. 2009; Cervelatti et al. 2013; Foy et al. 1999) and 2 reported no difference (Ahlskog et al. 1995; Iuliano et al. 2010). On pooled analysis, sUA was lower in AD compared to controls with SDM −0.42 (95 %CI) (Fig. 2).

VaD Four studies found sUA levels to be lower in cases (Foy et al. 1999; Maesaka et al. 1993; Polidori et al. 2004; Tohgi et al. 1993), and one found no difference (Matsubayashi et al. 1988). In studies including patients with stroke, sUA levels were higher in cases (Wei et al. 2012; Qin and Yang 2009). There was no apparent difference in sUA between cases of VaD and controls across seven studies (SDM −0.05) (95 %CI, $p = 0.908$) (Fig. 2).

PDD Five studies found sUA levels to be lower in cases (Foy et al. 1999; Maetzler et al. 2011; Tohgi et al. 1993; Wen et al. 2012; You and Liu 2012), and three found no difference (Ahlskog et al. 1995; Annanmaki et al. 2011; González-Aramburu et al. 2014). Pooled analysis of seven studies suggested lower sUA in PDD with SDM −0.67 (95 %CI, $p = 0.001$) (Fig. 2).

MCI Two studies found sUA levels to be lower in cases (Baldieras et al. 2008; Rinaldi et al. 2003); one found levels to be higher (Cervelatti et al. 2013) and one found no difference (Iuliano et al. 2010). There was no apparent difference on pooled analysis (SMD −0.24) (95 %CI) (Supplementary materials).

Mixed or unspecified dementia Three studies found levels to be higher in cases (Cicero et al. 2014;

Table 1 Studies including patients with Alzheimer's Disease and Vascular Dementia

Ref.	Disease population	Country	Design	Control population	*n*, cases/ controls	SUA compared in cases/controls	Cog. function related to SUA	Longitudinal follow-up
Ahlskog et al. (1995)	AD; PD	USA	Case-control	Normal controls	71/15	Yes	No	No
Baldieras et al. (2008)	AD; MCI	Portugal	Case-control	Healthy age matched	127/37	Yes	No	No
Bowman et al. (2010)	AD	USA	Cohort	No	32/NA	No	Yes	Yes
Can et al. (2013)	AD	Turkey	Case-control	Age / gender matched	32/32	Yes	Yes	No
Cankurtaran et al. (2013)	AD	Turkey	Case-control	Age and gender matched	143/1553	Yes	Yes	No
Cascalheira et al. (2009)	AD	Portugal	Case-control	Healthy older adults	19/36	Yes	No	No
Cervelatti et al. (2013)	AD; MCI	Italy	Case-control	Older adults	235/99	Yes	No	No
Foy et al. (1999)	AD; VD; PDD	UK	Case-control	Age matched	134/58	Yes	No	No
Gackowski et al. (2008)	AD	Poland	Case-control	Age matched	18/33	Yes	No	No
Irizarry et al. (2009)	AD	USA / Canada	Cohort	No	204/NA	No	Yes	Yes
Iuliano et al. (2010)	AD; MCI	Italy	Case-control	Healthy controls	90/24	Yes	No	No
Kasa et al. (1989)	AD	USA	Case-control	Other dementias	47/71	Yes	No	No
Kim et al. (2006)	AD	Korea	Cross-sectional	Healthy controls	101/101	Yes	No	No
Wei et al. (2012)	Stroke, CI	China	Case-control	Stroke, no CI	34/88	Yes	Yes	No
Maesaka et al. (1993)	AD; VD	USA	Case-control	Healthy controls	AD 18 VD 6/11	Yes	No	No
Matsubayashi et al. (1988)	VD	Japan	Case-control	Cerebral infarcts no dementia	24/27	Yes	No	No
Polidori and Meococci (2002)	AD, female	Germany	Cross-sectional	Age matched healthy females	35/40	Yes	No	No
Polidori et al. (2004)	AD; VD	Germany	Cohort	Healthy controls	AD 63 VD 23/55	Yes	No	No
Pulido et al. (2005)	AD	Spain	Case-control	No cognitive damage	20/22	Yes	No	No
Qin and Yang (2009)	Stroke, CI	China	Cross-sectional	Stroke, CI	26/72	Yes	No	No
Rinaldi et al. (2003)	AD; MCI	Italy	Case-control	Elderly adults attending hospital	AD 63 MCI 25/56	Yes	No	No
Shang et al. (2009)	AD	China	Case-control	Healthy Controls	30/30	Yes	No	No
Tohgi et al. (1993)	AD; VD	Japan	Case-control	Not defined	25/14	Yes	No	No
Wen et al. (2012)	Delirium, dementia, others	China	Case-control	Healthy controls	64/42	Yes	No	No
Wikkelso et al. (1981)	AD; VD	Sweden	Cross-sectional	No	38	No	No	No
Zafrilla et al. (2006)	AD	Spain	Case-control	Healthy controls	66/27	Yes	Yes	No

AD Alzheimer's disease, *VD* Vascular Dementia, *PD* Parkinson's Disease, *CI* cognitive impairment, *MCI* mild cognitive impairment, *NA* not applicable

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Ruggiero Cherubini et al. 2009; Wen et al. 2012). One paper (Li et al. 2010) studied males and females independently: in the male population, sUA levels were found to be lower and within the female population, no difference was seen. Across four studies, there was no apparent difference between groups (SDM 0.19) (95 %CI, $p = 0.304$) (Fig. 2).

Association of sUA and measures of cognitive function

Twenty-four cross-sectional studies (Vanorsdall et al. 2008; Afsar et al. 2011; Annanmaki et al. 2008; Ascherio et al. 2009; Baldieras et al. 2008; Bowman et al. 2010; Can et al. 2013; Cankurtaran et al. 2013; Cicero et al. 2014; González-Aramburu et al. 2014; Irizarry et al. 2009; Li et al. 2010; Wei et al. 2012; Madan et al. 2007; Maetzler et al. 2011; Moccia et al. 2014; Pan et al. 2013; Ruggiero Cherubini et al. 2009; Schretlen et al. 2007; Verhaaren et al. 2013; Wang et al. 2009; Wu et al. 2013; Yoldas et al. 2010; Zafrilla et al. 2006) ($n = 9999$ with 6045 with cognitive impairment/dementia) compared sUA to a measure of cognitive function (eTable 4). Two papers describing PDD used the same cohort and so only the primary dataset was used in analysis. Various approaches were used to describe association of sUA and cognition.

All cause dementia/cognitive impairment Results were conflicting, with two papers (Pan et al. 2013; Wu et al. 2013) suggesting a positive correlation between sUA and MMSE, three papers (Afsar et al. 2011; Cicero et al. 2014; Wei et al. 2012) suggested negative correlation, and six papers (Annanmaki et al. 2008; Baldieras et al. 2008; Bowman et al. 2010; González-Aramburu et al. 2014; Maetzler et al. 2011) suggested no correlation. Two papers described levels of sUA across dementia severity groupings, with one paper (Cankurtaran et al. 2013) suggesting lower sUA in severe disease and the other reporting no association (Zafrilla et al. 2006). Four papers performed regression analysis with cognitive function as the dependent variable and sUA as a predictor, one study (Moccia et al. 2014) found higher sUA to be associated with better performance in cognitive tests, two found higher sUA to be associated with poorer

Table 2 Studies Including Patients with PD

Ref.	Disease population	Country	Design	Control population	*n*, Cases/controls	SUA compared in cases/controls	Cog function related to SUA	Longitudinal follow-up
Ahlskog et al. (1995)	AD; PD	America	Case Control	Normal controls	71/15	Yes	No	No
Annanmaki et al. (2008)	PD	Finland	Cross Sectional	No	40/NA	No	Yes	No
Annanmaki et al. (2011)	PD	Finland	Cohort	Yes	28/12	Yes	Yes	Yes
Ascherio et al. (2009)	PD	America	Clinical Trial Analysis	No	774/NA	No	Yes	No
Foy et al. (1999)	AD; VD; PD with dementia	UK	Case Control	Age matched	134/41	Yes	No	No
González-Aramburu et al. (2014)	PD, CI	Spain	Case Control	PD, no CI	72/271	Yes	Yes	No
Maetzler et al. (2011)	Lewy-Body Disorders	Germany	Case Control	Healthy controls	171/76	Yes	Yes	No
Moccia et al. (2014)	PD	Italy	Cross Sectional	No	80/NA	No	Yes	No
Pan et al. (2013)	PD	China	Case Control	Age matched	160/80	No	Yes	No
Tohgi et al. (1993)	PD	Japan	Case Control	Age matched	26/14	Yes	Yes	No
Wang et al. (2009) Jun 16	PD, CI	China	Case Control	PD, no CI	54/54	Yes	Yes	No
You and Liu 2012	PD with depression or CI	China	Case Control	PD without depression or CI	29/26	Yes	No	No

AD Alzheimer's disease, *VD* Vascular Dementia, *PD* Parkinson's Disease, *CI* cognitive impairment, *NA* not applicable

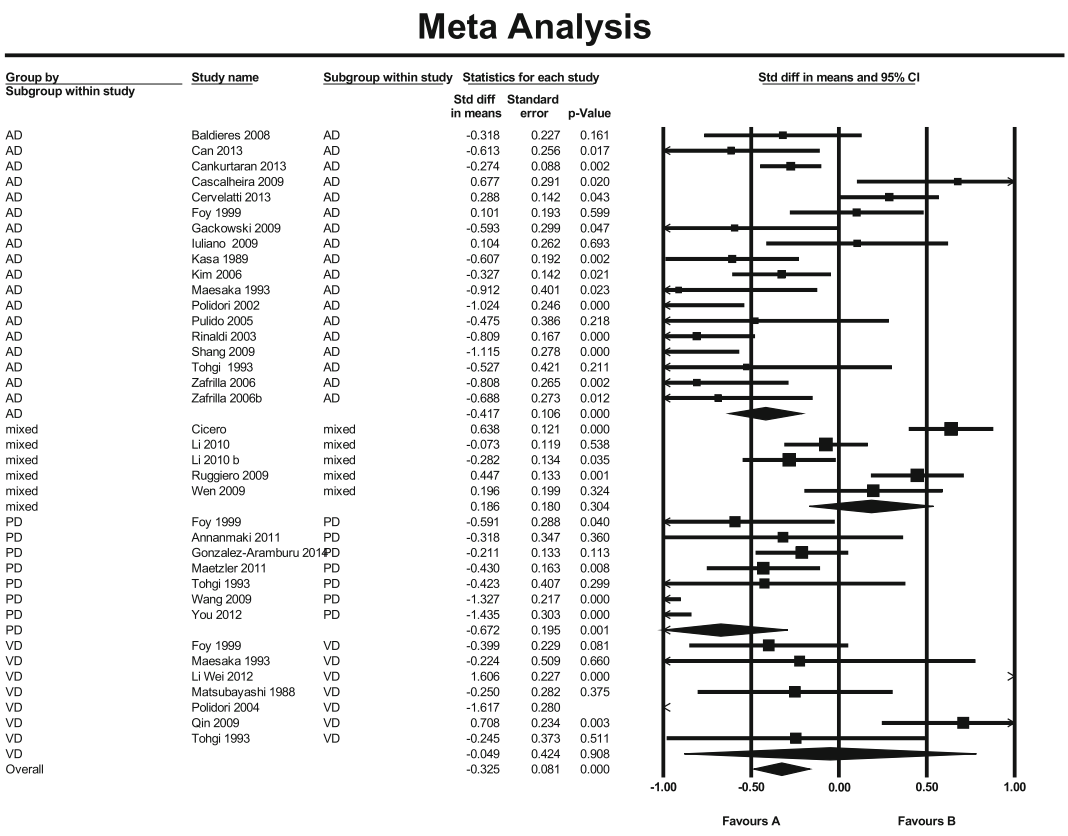

Fig. 2 Meta analysis of sUA level in cases of dementia versus controls by dementia group

performance (Madan et al. 2007; Wen et al. 2012) ($n=1508$), and one found no relationship (Zafrilla et al. 2006). Twelve papers ($n=4134$ participants) presented a form of correlation analysis using Pearson product moment correlation coefficient (Afsar et al. 2011; Annanmaki et al. 2011; Annanmaki et al. 2008; Baldieras et al. 2008; Bowman et al. 2010; Can et al. 2013; Cicero et al. 2014; González-Aramburu et al. 2014; Li et al. 2010; Wei et al. 2012; Maetzler et al. 2011; Pan et al. 2013; Wu et al. 2013), 11 of which used the MMSE and were suitable for pooled analysis (Afsar et al. 2011; Annanmaki et al. 2008; Baldieras et al. 2008; Bowman et al. 2010; Can et al. 2013; Cicero et al. 2014; González-Aramburu et al. 2014; Li et al. 2010; Wei et al. 2012; Maetzler et al. 2011; Pan et al. 2013; Wu et al. 2013) (eTable 5). Included patients were heterogeneous (AD $n=2$ studies; PDD $n=4$ studies; "healthy" older adults $n=2$). There was no suggestion of correlation between sUA and MMSE across the body of studies ($r=-0.084$) ($p=0.274$) (Supplementary materials).

PDD Across four studies with PDD (Annanmaki et al. 2008; González-Aramburu et al. 2014; Maetzler et al. 2011; Pan et al. 2013), a positive correlation between sUA and MMSE was apparent ($r=0.155$; $p=0.003$) (eTable 6). There was no evidence of potential publication bias across the ten studies ($p=0.326$ on Egger's regression intercept) (Supplementary materials).

Time series analyses of sUA and cognitive function

Four studies reported the relationship between sUA and cognitive function over time (Table 3). The heterogeneity in study methodology and reporting precluded quantitative analyses. One paper (Gackowski et al. 2008) ($n=4618$ participants) reported lower risk of incident dementia across increasing quartiles of sUA in a healthy population cohort. One paper (Kasa et al. 1989) ($n=747$ participants) reported risk of incident dementia across quintiles of sUA in an MCI cohort with no relationship reported. The remaining two papers were modest in size

Table 3 Time series analyses of serum and cognitive function

Ref	Population studied	Number of subjects	Analysis performed	Summary result
Euser et al. (2009)	Population cohort	4618	Cox proportional hazards model for HR for sUA (quartiles) and risk of dementia	HR for dementia 0.73 (95 % CI 0.55 to 0.97) for highest vs. lowest quartile of sUA
Annanmaki et al. (2011)	PD	28	Correlation between baseline sUA and cognitive function at 3 years (neuropsychological battery).	No correlation with any measure
Irizarry et al. (2009)	MCI	747	1. Survival analysis for survival free of AD across quintiles of sUA 2. Interaction between sUA and rate of cognitive decline (ADAS-cog)	1. No relationship between sUA and progression to AD. 2. Low plasma urate associated with faster cognitive decline ($p = 0.008$ for interaction term sUA × time)
Bowman et al. (2010)	AD	32	Correlation between baseline sUA and annual change in cognition (ADAS, MMSE, CDR)	No correlation

HR hazard ratio, *sUA* serum Uric Acid, *ADAS* Alzheimer's disease Assessment Scale, *MMSE* Mini-mental state exam, *CDR* Clinical Dementia Rating

((Annanmaki et al. 2011) ($n = 40$ participants) (Cankurtaran et al. 2013) ($n = 32$ participants)) and described no association with sUA and change in cognitive function over time.

Discussion

Using systematic review and meta-analyses, we offer a synthesis of the literature describing the relationship between sUA and dementia/cognitive impairment. Although many relevant papers were available, there was substantial heterogeneity and risk of various biases. Accepting this important caveat, we can draw some cautious conclusions. Association between sUA and dementia/cognitive impairment was weak across undifferentiated dementia groups; however, when described according to underlying pathology, there appeared to be a stronger association with AD and PDD than with VAD. This relationship was seen in both case-control and correlational analyses.

Our findings would support an association between sUA and cognitive function/dementia but the relationship is complex with sUA potentially damaging in context of vascular disease (stroke, small vessel cerebrovascular disease) and potentially neuroprotective (hydrophilic antioxidant properties) in other settings. This paradox has a biological plausibility. In vivo, ingested and endogenously synthesized purines are metabolized, via the action of xanthine oxidase, to xanthine and then sUA. The action of xanthine oxidase yields hydroxyl free radicals and hydrogen peroxide which can add to or initiate oxidative stress. Thus, despite sUA itself being antioxidant, its generation in vivo is associated with an oxidative stress (Dawson and Walters 2006).

Strengths and limitations of included studies

The majority of included studies were graded as high risk of bias. The weakest study design for investigating association is case-control due to the potential to inflate estimates by including phenotypic extremes. The majority of data available used a case-control approach. Correlation of sUA with a cognitive test score provides useful data but offers no information on potential direction of association or causation. A more informative study design would be prospective follow-up of a cohort free from dementia at baseline. Few studies used this approach, where sUA was related to temporal change in cognitive function; the largest (and highest quality) study in our review suggested that higher sUA level was associated with reduced risk of incident dementia.

Association between sUA and cognitive outcomes could be confounded by a number of other related factors, for example, age, diet, and medication can all impact on sUA and cognition (Choi et al. 2004; Reyes 2003). Few studies adequately corrected for confounders. It is interesting that while simple case-

control studies suggested an association, pooled analysis of studies that used multivariable regression to assess for independent associations reported a neutral result.

Strengths and limitations of the review and analyses

We used a robust search strategy informed by an experienced team and employing validated search strings. We followed best practice guidance in conduct and reporting and included multiple internal and external "quality control" measures. We were aware that several Chinese studies had been conducted in the field and so imposed no language restriction and purposively searched specific Chinese resources.

There are limitations in our approach. Our dementia phenotyping was necessarily pragmatic. We used those diagnostic labels employed in the original papers. Diagnostic classification has evolved over time and clinical diagnosis is often inexact, for example, many labeled AD may have a vascular component. To facilitate summary analyses, we grouped diagnostic labels, but we recognize that this approach is potentially problematic, for example, we classed studies of post-stroke dementia under the rubric "vascular dementia" although the two states are not synonymous and we grouped dementias with parkinsonian phenotype together, but accept that within this group there is potential pathophysiological heterogeneity. It is of interest that the two studies that specifically looked at post-stroke cognitive decline suggested an association with sUA that was the converse of the other studies.

We used various meta-analytical techniques to offer a summary of the complex literature. With the various biases and heterogeneity, these analyses need to be treated with caution and should be regarded as hypothesis-generating, rather than definitive. Even when pooling studies, total numbers may still have been too small to show real but modest associations.

Implications for research and practice

Further study of sUA and cognition is warranted, but basic approaches such as uncorrected case-control analyses are unlikely to progress our understanding. Given the potential issues of confounding, there may be a role for a Mendelian randomization approach, incorporating fixed genetic information into the traditional epidemiological study design to provide suggestive information on causality free from the usual lifestyle and environmental confounders. Use of large clinical registries may also be informative; linking prescribing data and national morbidity/mortality records have allowed investigators to describe links between sUA lowering medications and cardiovascular outcomes across whole populations. A similar paradigm could be used for cognitive outcomes.

Our findings offer potential new avenues for investigating the pathophysiology of cognitive decline; however, data are not sufficiently robust to suggest direct clinical applications. Randomized controlled trials of sUA lowering and vascular outcomes are ongoing, and it will be of interest to see cognitive outcomes in these studies.

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Author contributions Dr Khan—study design, data acquisition, analysis, interpretation, critical revision
Dr. Quinn—study design, data acquisition, analysis, interpretation, critical revision
Dr. Hewitt—study design, interpretation, critical revision
Dr. Fan—data acquisition, interpretation, and critical revision
Dr. Dawson—study design, data acquisition, analysis, interpretation, critical revision, and study supervision

Compliance with ethical standards

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