



# Association between serum uric acid level and multiple system atrophy: A meta-analysis

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## ABSTRACT

**Objectives:** Lower serum uric acid (UA) levels are considered to be related to the risk to develop many neurodegenerative disorders. However, the association between serum UA level and multiple system atrophy (MSA) remains controversial. The aim of this meta-analysis was to evaluate the relationship between serum UA level and MSA.

**Patients and methods:** PubMed, Web of Science, Embase, Cochrane Library and China National Knowledge Infrastructure (CNKI) were searched for eligible studies. Standardized mean difference (SMD) and 95% confidence intervals (95% CI) were calculated in a fixed-effects model or a random-effects model when appropriate. Subgroup analyses were carried out based on gender. A total of 6 eligible studies involving 547 MSA patients and 637 healthy individuals were identified.

**Results:** Meta-analysis results revealed that individuals with MSA had lower sera levels of UA as compared with healthy controls (pooled SMD is  $-0.51$ , 95%CI:  $-0.88$  to  $-0.14$ ;  $p = 0.006$ ). The subgroup analysis to detect sex differences showed that the pooled SMD was  $-0.61$  (95% CI:  $-0.82$  to  $-0.40$ ;  $p < 0.0001$ ) for males and  $-0.22$  (95% CI:  $-0.55$  to  $0.10$ ;  $p = 0.18$ ) for females compared with healthy controls.

**Conclusion:** Our meta-analysis revealed that lower serum level of UA is associated with an increased risk of MSA and the relationship is significant in men but not in women.

## 1. Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset neurodegenerative movement disorder, characterized by autonomic dysfunction in combination with parkinsonism or cerebellar ataxia [1,2]. The prevalence of MSA adjusted to the WHO European standard population  $\geq 40$  years of age ranges from 3.7 to 14.6 per 100,000 individuals [3]. The etiology of MSA remains unclear, but oxidative stress and mitochondrial dysfunction have been strongly implicated [4]. It is well documented that uric acid (UA) may be neuroprotective in many neurodegenerative disorders such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), via its antioxidant effect [5,6]. As a typical antioxidant, UA has been also widely demonstrated to be associated with MSA in many studies [7–9]. However, the correlation between serum UA level and MSA remains controversial. Several studies have revealed a negative relationship between serum UA level and MSA [8,10–13], while other groups did not find a correlation between

high serum UA levels and reduced risk of MSA [14]. Therefore, the relationship between circulating UA and MSA incidence needs to be further evaluated. We conducted this meta-analysis to quantitatively evaluate the relationship between serum UA levels and risk of MSA. On the one hand, it is essential for the early screening and prevention of MSA by identifying the risk factors for the development of MSA. On the other hand, the identification of the relationships between MSA and modifiable risk factors can provide us appropriate evidence for the development of new therapies for MSA.

## 2. Materials and methods

### 2.1. Literature search

A systematic literature search was conducted on literature published up to February 18th, 2017 concerning the association of serum UA levels with the risk of MSA using PubMed, Web of Science, Embase,

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Cochrane Library and China National Knowledge Infrastructure (CNKI). No language restriction was set. Search terms were ("Multiple system atrophy" or "Multisystem atrophy") and ("uric acid" or "Urate"). Irrelevant studies were discarded and those potentially eligible studies were evaluated by two independent investigators (Xi Zhang and De-Shan Liu) for their inclusion.

## 2.2. Inclusion criteria

All included studies must meet the following criteria: (1) study design limited to case-control studies, cohort studies or cross-sectional studies; (2) focus upon assessment of the relationship between serum UA level and MSA; (3) the inclusion of healthy subjects as controls; (4) serum UA levels were evaluated with appropriate methods.

## 2.3. Exclusion criteria

The following publications were excluded from the analysis: (1) studies concentrating on non-serum uric acid, such as cerebrospinal fluid uric acid; (2) studies that did not report the exact values of serum UA level; (3) studies with obvious error of unit; (4) studies whose data had been repeatedly published.

## 2.4. Data extraction and quality assessment

Data was extracted from each study by two independent reviewers. The following data were recorded: Family name of the first author, the year of publication, the number of cases and controls, their sex, the mean serum UA levels for cases and controls and the standard deviation (SD) of serum UA levels for cases and controls.

The quality of included studies was assessed strictly with the well-known Newcastle–Ottawa Scale (NOS). Studies with overall NOS  $\geq 7$  were considered as high-quality study [15].

## 2.5. Statistical analysis

We evaluated the relationship between serum UA level and the risk of MSA with standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity analysis was performed using the chi-square test and  $I^2$  statistic, with  $p \leq 0.05$  and a  $> 50\%$  threshold for the  $I^2$  statistic indicating significant heterogeneity [16]. SMD were pooled by the random effects model when significant heterogeneity was present. Subgroup analyses and sensitivity analysis were used for exploring the source of heterogeneity. The meta-analysis was conducted using the Cochrane Collaboration Review Manager (RevMan version 5.3). To evaluate the publication bias, we performed the Egger's test using Stata 12.0 (Stata Corp LP, College Station, TX, USA) as a funnel plot is applied when 10 or more studies are available as suggested by Cochrane Handbook.

## 3. Results

### 3.1. Search results and characteristics of the included studies

We initially identified 82 potentially relevant studies by computerized search (Fig. 1). After excluding duplicate articles, reviews and those studies not addressing the subject of interest, 14 papers remained. Further exclusions included the removal of four articles featuring a study design not encompassed by our inclusion criteria; two studies were excluded for a failure to report exact values of serum UA level; one study was excluded due to a lack of clarity regarding the initiation and deadline of data collection [10], indicating that the data might have been repeatedly published in subsequent reports; another study was excluded for obvious error of unit. The remaining 6 studies, containing data from a total of 547 MSA patients and 637 healthy individuals, satisfied inclusion criteria, and were included for meta-analysis

[8,10–14,27]. The ages and serum UA levels of individuals in included studies were presented as mean  $\pm$  SD. The characteristics of the included studies are summarized in Table 1.

### 3.2. Meta-analysis results

Subjects with MSA had lower levels of serum UA when compared with healthy controls. The pooled SMD is  $-0.51$  (95%CI:  $-0.88$  to  $-0.14$ ;  $p = 0.006$ ) (Fig. 2). The random effects model was applied because significant heterogeneity across studies was detected ( $I^2 = 88\%$ ;  $P < 0.00001$ ).

### 3.3. Publication bias

Publication bias was assessed by Egger's test and no statistical publication bias was detected ( $p = 0.329$ ).

### 3.4. Sensitivity and subgroup analysis

We performed sensitivity analysis by omitting individual studies from the meta-analysis. The pooled results show that serum UA levels were still significantly lower in MSA patients than those in healthy controls.

Subgroup analysis was stratified by gender. The characteristics of subgroup analysis based on gender are summarized in Table 2. The pooled results of subgroup analysis for sex differences were consistent with the overall meta-analysis. The subgroup analysis accounting for gender showed that the pooled SMD was  $-0.61$  (95% CI:  $-0.82$  to  $-0.40$ ,  $p < 0.0001$ ) for males and  $-0.22$  (95% CI:  $-0.55$  to  $0.10$ ,  $p = 0.18$ ) for females as compared with healthy controls in a fixed-effect model (Fig. 3). The overall heterogeneity continued to be substantial in subgroup analysis based on gender ( $I^2 = 63\%$ ;  $P = 0.02$ ). Heterogeneity was still found in women ( $I^2 = 35\%$ ;  $P = 0.22$ ) but not in men ( $I^2 = 0\%$ ;  $P = 0.47$ ) (Fig. 3).

## 4. Discussion

Our meta-analysis indicated an inverse correlation between serum UA levels and the risk of MSA. It is similar to the results of many previous studies on PD, another synucleinopathy [5,17–19]. To the best of our knowledge, no meta-analysis has been published so far to address the relationship between serum UA levels and the risk of MSA. Although the exact mechanism underlying the association between serum UA levels and the pathogenesis of MSA remains unclear at present, UA has been strongly documented as an important endogenous antioxidant implicated in the development and progression of MSA [4,7,14,20–22]. UA has been considered to be a strong scavenger of various reactive nitrogen species (RNS) and reactive oxygen species (ROS) [23,24]. Increased serum ROS/RNS levels were reported to develop MSA [25]. Thus, we speculated that the decreased serum UA levels in MSA patients may be caused by increased consumption of UA as a scavenger for enhanced serum ROS/RNS levels. But further research needed to verify the assumption. According to the results of subgroup analysis based on gender, we found significant association between lower serum UA level and MSA in male but not in female. We speculated that the difference may be related to oestrogen, but more large sample studies needed to confirm this new conclusion.

There are several potential weaknesses in our present study, which should not be ignored: (1) The foremost drawback is the number of studies included is limited; (2) We fail to conduct a subgroup analysis to find the differences between MSA-C (cerebellar type) and MSA-P (parkinsonism type) in the association between lower serum UA level and MSA for the limited data. (3) Serum UA levels tend to be lower in females than males, which has been linked to higher plasma oestrogen levels. Our present study is unable to evaluate the biological basis underlying the gender differences revealed by the meta-analysis. (4) Other

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