



## Short report

## Higher baseline serum uric acid is associated with poorer cognition but not rates of cognitive decline in women

Tracy D. Vannorsdall<sup>a,b,\*</sup>, Alexandra M. Kueider<sup>c</sup>, Michelle C. Carlson<sup>c,d</sup>, David J. Schretlen<sup>a,e</sup><sup>a</sup> Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 N. Wolfe St. Baltimore, MD 21287, USA<sup>b</sup> Department of Neurology, The Johns Hopkins University School of Medicine, 600 N. Wolfe St. Baltimore, MD 21287, USA<sup>c</sup> Department of Mental Health, The Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205, USA<sup>d</sup> Center on Aging and Health, The Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205, USA<sup>e</sup> Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, 600 N. Wolfe St. Baltimore, MD 21287, USA

## ARTICLE INFO

## Article history:

Received 8 July 2014

Received in revised form 18 September 2014

Accepted 28 October 2014

Available online 29 October 2014

Section Editor: Christian Humpel

## Keywords:

Serum uric acid

Cognitive function

Cognitive aging

Aging

Cerebrovascular disease

Neuropsychology

## ABSTRACT

Serum uric acid is a powerful antioxidant that may have neuroprotective properties. While some studies have found that greater serum uric acid is associated with better cognition in older adults, it is also associated with numerous vascular risk factors that increase risk for dementia. Women may also be particularly vulnerable to the vascular effects of elevated uric acid. We previously found that mildly elevated serum uric acid is a biomarker of cognitive dysfunction in older adults, and that this likely is mediated by cerebral ischemic burden. Here we examine both cross-sectional and longitudinal associations between serum uric acid, and declines in cognition and functioning in 423 cognitively healthy community-dwelling older women in the Women's Health and Aging Study (WHAS II). We hypothesized that higher serum uric acid would be associated with poorer concurrent functioning and greater declines over 9 years. In linear regression analyses, higher baseline serum uric acid was associated with poorer working memory, with a trend toward slower manual speed and dexterity before and after adjusting for baseline serum uric acid, demographic and health/cardiovascular variables. However, there were no associations for global cognitive functioning, learning/memory, sequencing, verbal fluency, or visuomotor construction. Mixed effects models also revealed no association with subsequent cognitive declines. Future research should examine changes in serum uric acid at earlier periods in the lifespan and their relationships with later cognitive declines.

© 2014 Elsevier Inc. All rights reserved.

## 1. Introduction

Uric acid is a byproduct of purine metabolism generated during the enzymatic degradation of xanthine and accumulates in the kidney. Its relationship to later-life cognitive functioning seems contradictory in that uric acid appears to have neuroprotective properties, yet it is associated with diseases that can cause cognitive dysfunction and dementia. There are several potential mechanisms for uric acid's seemingly contradictory relationship with cognitive functioning.

On the one hand, serum uric acid is the most abundant natural antioxidant in human plasma. Its antioxidant properties might protect against free radical damage, thereby reducing the risk of oxidative stress-related cognitive impairment and dementia (Zhu et al., 2004). Consistent with this, serum uric acid levels are lower in persons with mild cognitive impairment (MCI) and Alzheimer's disease than in healthy controls (Rinaldi et al., 2003). Low serum uric acid also is linked to accelerated cognitive declines in those with MCI (Irizarry et al., 2009)

further suggesting that higher levels can be neuroprotective. On the other hand, for each molecule of uric acid produced, the enzymatic degradation of xanthine simultaneously produces superoxide anions, which are among the most powerful pro-oxidants known. While uric acid normally is produced in the liver and small bowel, it can be produced by the brain in the presence of ischemia (Phillis, 1994). Thus, uric acid might be beneficial, while the processes involved in its production are detrimental (Schretlen et al., 2007b).

Recently, higher uric acid was associated with poorer processing speed and executive functioning as well as greater white matter atrophy in Rotterdam Scan study participants (Verhaaren et al., 2013). We previously found a similarly deleterious association between mildly elevated serum uric acid and brain structure and function. In a series of cross-sectional observational studies, community-dwelling adults with uric acid levels in the upper end of the normal range were 2.7 to 5.9 times more likely to score in the lowest quartile on measures of processing speed, verbal memory, and working memory (Schretlen et al., 2007a). In a follow-up investigation higher serum uric acid levels were associated with significantly greater cerebral ischemia as indexed by white matter hyperintensity volumes (Schretlen et al., 2007b). This association was most pronounced among those aged 60 or older wherein the

\* Corresponding author at: Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer 218, Baltimore, MD 21287, USA.

E-mail address: [TVannor1@jhmi.edu](mailto:TVannor1@jhmi.edu) (T.D. Vannorsdall).

odds of cerebral ischemic burden were increased 4- to 5-fold. In the third study of our series we demonstrated that individual differences in cerebral ischemia mediate the previously observed associations between serum uric acid and mild cognitive dysfunction (Vannorsdall et al., 2008).

Most published studies of serum uric acid and cognition have included both sexes. There is growing appreciation that uric acid may have different relationships with disease and outcomes in women and men. For example, the relationship between uric acid and cardiovascular disease and mortality is stronger in women (Alderman et al., 1999; Fang and Alderman, 2000), including postmenopausal women (Park et al., 2012). Heo and colleagues (2010) found that higher uric acid is a strong independent risk factor for brain infarction and exerts a dose–response relationship exclusively in women. Higher uric acid is also associated with reduced rates and progression of Parkinson's disease in men, but it shows an opposite trend in women (O'Reilly et al., 2010).

In short, while previous research has yielded strikingly contradictory findings, there is some evidence that even mild elevations of serum uric acid are associated with the development of cerebral ischemia, white matter atrophy, and cognitive dysfunction. Women may be more vulnerable to the vascular effects of elevated uric acid than men. Our initial findings were based on a relatively small sample that included both sexes, and the observed relationships were strictly cross-sectional. Here we extend our prior findings by examining both cross-sectional and longitudinal associations between serum uric acid and cognition in a large sample of older, community-dwelling women. We hypothesized that higher serum uric acid would be associated with poorer concurrent cognitive functioning and greater cognitive declines over time.

## 2. Materials and methods

### 2.1. Study participants

The WHAS II is a prospective, longitudinal, population-based study of physical and cognitive functioning in a cohort selected from the highest functioning two-thirds of 70- to 79-year-old community-dwelling women residing in eastern Baltimore, Maryland. The sampling and recruitment of participants are described elsewhere (Carlson et al., 1999; Fried et al., 1999). Briefly, the sampling frame was defined as female medicare beneficiaries residing within 12 zip codes in the eastern half of Baltimore City and County. Participants were deemed eligible if they were: (1) 70–79 years old, (2) proficient in English, (3) able to complete a telephone interview, (4) achieved a Mini-Mental State Examination (MMSE) score of 24–30 at screening, and (5) reported difficulty in no more than one of the following: mobility/exercise tolerance (e.g., walking a half-mile), upper extremity function (e.g., lifting and carrying 10 lb), basic self-care (e.g., bathing), and instrumental activities of daily living (e.g., shopping).

Of 436 women who participated in the baseline assessment, baseline serum uric acid values were obtained for 423. Five follow-up examinations occurred at approximately 1.5, 3, 6, 7.5, and 9 years following the baseline assessment. Over the course of the study, 90 participants died (21%) and 103 were lost to follow-up (24%).

Each examination consisted of a comprehensive medical history, medication inventory, physical and neurological examinations, and neuropsychological testing. Women also underwent blood testing to assay serum uric acid, C-reactive protein, and interleukin-6. All participants gave written, informed consent at baseline, and the study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

### 2.2. Measurement of serum uric acid and cognition

Serum uric acid levels were assayed at visits one (baseline) through three. At each visit, serum was extracted and frozen at  $-80^{\circ}\text{C}$  until processed.

Trained research assistants administered all of the neuropsychological tests, descriptions of which can be found in (see Lezak et al., 2004; Schretlen et al., 2008 for neuropsychological test details). At each of the six visits, raw scores were recorded from a measure of global cognitive functioning, the Mini Mental State Exam (MMSE), Trail Making Test, parts A and B, which assess psychomotor speed and mental sequencing, word list learning over three trials and delayed word recall (Hopkins Verbal Learning Test-Revised; HVLT-R) and times to complete the Purdue Pegboard with both hands. A measure of auditory divided attention and working memory (Brief Test of Attention) was administered at visits one through three. At visits three through six, participants completed tests of processing speed (Pattern Comparison Test) and constructional praxis (Clock Drawing, to command and copy). From visits four through six, participants completed tests of simple auditory attention and working memory (Digit Span) and verbal fluency in response to both a letter cue and the category cue 'animals'. All cognitive outcomes were treated as continuous variables.

### 2.3. Statistical analyses

In addition to baseline uric acid, demographic, health and cardiovascular covariates in the models included age (in years), education (in years), race (white vs. black), body mass index (BMI), perceived health status ranging from 1 (excellent) to 5 (poor), hypertension, diabetes, stroke, alcohol use, use of diuretics, C-reactive protein, and interleukin-6 at baseline. See Table 1 for baseline demographic, health, and functional characteristics of study participants.

Linear multiple regression was used to model cross-sectional relationships between serum uric acid and global cognitive functioning as well as each cognitive outcome measure, adjusting for demographic and health characteristics mentioned previously. Continuous values of serum uric acid were included in each model regardless of its statistical significance. For outcomes measured from the study outset (MMSE, Trail Making Test parts A and B, HVLT-R learning and recall, Purdue Pegboard, Brief Test of Attention), baseline serum uric acid was used in the analyses. For cognitive tests that were first administered at visit three or four (Digit Span, Pattern Comparison Test, Clock Drawing, Verbal Fluency) the regression analyses used the concurrent visit three serum uric acid values.

Paired samples t-tests examined changes in cognitive test performance between the first and final study visits. Mixed effects models adjusting for (1) baseline serum uric acid, (2) baseline serum uric acid and demographic variables (age, race, education), and (3) baseline serum uric acid, demographic, health and cardiovascular variables were used to examine the longitudinal relationship between continuous cognitive and functional measures and baseline values of serum uric acid. An interaction between time and serum uric acid was included to determine whether rates of cognitive decline varied by levels of serum uric acid. All models were completed using PROC MIXED in SAS version 9.

**Table 1**  
Baseline demographic and health characteristics.

Characteristic	Mean (SD) or %
Age	73.9 (2.8)
Education, y	12.5 (3.4)
Race, % white	80.9%
BMI, kg/m <sup>2</sup>	26.7 (5.2)
Hypertension	48.7%
Diabetes	7.5%
Stroke	5.4%
Alcohol use	31.6%
Diuretic use	2.3%
C-reactive protein	5.3 (5.7)
Interleukin-6 (mg/dL)	4.1 (6.3)
Perceived health status	2.5 (0.9)

Download English Version:

<https://daneshyari.com/en/article/8263969>

Download Persian Version:

<https://daneshyari.com/article/8263969>

[Daneshyari.com](https://daneshyari.com)