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# Higher Baseline Serum Uric Acid is Associated with Poorer Cognition but Not Rates of Cognitive Decline in Women

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## 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 towards 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 visuoconstruction. Mixed effects



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**Conflict of Interest**
The authors have no conflicts of interests.

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.

**Keywords**

Serum uric acid; cognitive function; cognitive aging; aging; cerebrovascular disease; neuropsychology

## 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 and others 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 and others 2003). Low serum uric acid also is linked to accelerated cognitive declines in those with MCI (Irizarry and others 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 and others 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 and others 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 and others 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 and others 2007b). This association was most pronounced among those aged 60 or older wherein the 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 and others 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 and others 1999; Fang and Alderman 2000), including postmenopausal women (Park and others 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 and others 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 and others 1999; Fried and others 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 pounds), 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 visit one (baseline) through three. At each visit, serum was extracted and frozen at −80°C until processed.

Trained research assistants administered all of the neuropsychological tests, descriptions of which can be found in (see Lezak and others 2004; Schretlen and others 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 visit 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.

## 3. Results

Baseline serum uric acid ranged from 1.9 to 12.5 mg/dL. Most participants had serum uric acid levels within the normal range of 2.4 to 6.0 mg/dL at baseline (n = 312, Mean = 4.76 mg/dL, SD = 0.84) (Fischbach and Dunning 2009). Another 4 had lower than normal baseline serum uric acid (Mean = 1.98 mg/dL, SD = 0.5), whereas 107 participants had higher than normal serum uric acid at baseline (Mean = 7.27 mg/dL, SD = 1.1). Serum uric acid levels remained relatively stable over the first three study visits ($r = 0.73$, $p < 0.0001$).

As shown in Table 2, baseline serum uric acid was not associated with global cognitive functioning (MMSE) in any of the models. In models adjusting for baseline serum uric with and without demographic variables, higher baseline serum uric acid was associated with poorer performance on tests of manual speed and dexterity and working memory. Similarly, in fully adjusted models, higher baseline serum uric acid was associated with poorer performance on a test of attention and working memory (Brief Test of Attention, $p = 0.048$), with a trend towards slower manual speed and dexterity (Purdue Pegboard test, $p = 0.068$).

Cognition declined between the first and last study visits for most cognitive outcomes. Performance on the Brief Test of Attention remained stable and Digit Span performance improved over time (see Table 3).

In longitudinal models, there were no serum uric acid-by-time interactions, indicating that baseline uric acid levels did not predict rates of cognitive decline.

## 4. Discussion

In a relatively large sample of initially healthy, older, community-dwelling women, the present analyses reveal that higher baseline serum uric acid was associated with poorer attention and working memory, and with a trend toward slower manual speed/dexterity after accounting for demographic and health characteristics. These findings are consistent with previous reports that higher levels of serum uric acid are associated cross-sectionally with poorer attention and working memory, psychomotor speed, and executive functioning (Schretlen and others 2007, Verhaaren and others 2013). They also are consistent with evidence that higher levels of serum uric acid correlate with greater white matter atrophy (Verhaaren and others 2013) and cerebral ischemic burdened as measured by the volume of hyperintense signal on T2-weighted brain MRI scans of older adults (Schretlen and others 2007), which likely mediates the relationship between increased serum uric acid and cognitive dysfunction (Vannorsdall and others 2008).

Contrary to our hypothesis, higher baseline levels of uric acid were not associated with greater cognitive decline over time. At baseline, one-quarter of the study participants had elevated serum uric acid. Given that serum uric acid levels were relatively stable over time, it is possible that baseline elevations in uric acid occurred in midlife or earlier in late life, causing brain changes (Vannorsdall and others 2008; Verhaaren and others 2013) that

produced subtle cognitive decline prior to study enrollment. In order to clarify this, it would be helpful to assay serum uric acid in relation to cognition longitudinally in a sample of younger adults as they transition from normal to hyperuricimic status.

These findings should be interpreted in the context of potential limitations. First, measuring plasma urate twice may not capture long-term exposure because of variability in hormone use during and after menopause. While we did see relative stability in uric acid values over a three year period, greater variability may have been present earlier in the period of older adulthood at which time vascular changes may have developed. Additionally, all of our participants were healthy and functionally intact at baseline. As such, these results may not generalize to all community-dwelling women. Factors such as physical activity, diet, and genetic vulnerability to cognitive decline were also not included. Strengths of the study include the use of a relatively large population-based sample in a longitudinal design that simultaneously evaluated numerous cognitive domains and functional outcome measures over a six-to-nine year interval.

## 5. Conclusions

Among initially healthy older community-dwelling women, higher baseline serum uric acid is associated with concomitant reductions in working memory and processing speed. However, baseline serum uric acid levels in older women were not associated with subsequent cognitive or functional declines. Future research should examine changes in serum uric acid at earlier periods in the lifespan and their relationships with later cognitive and functional declines.

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## Highlights

- Serum uric acid has conflicting associations with late-life cognitive functioning.
- It is associated with cerebral ischemia and poorer cognition cross-sectionally.
- Women may be especially vulnerable to the vascular effects of elevated uric acid.
- We explored longitudinal associations with cognition in WHAS II participants.
- Uric acid correlated inversely with cognition at baseline but not longitudinally.

**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$^2$ | 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) |

**Table 2**

Cross-sectional associations between baseline serum uric acid and cognitive functioning after adjusting for baseline serum uric acid, demographic, and health variables.

| | Baseline Uric Acid | | Baseline Uric Acid & Demographics | | Baseline Uric Acid, Demographics, & Health | |
|---|---|---|---|---|---|---|
| **Outcome** | **Estimate (SE)** | **P-value** | **Estimate (SE)** | **P-value** | **Estimate (SE)** | **P-value** |
| MMSE | −0.08 (0.06) | 0.19 | 0.001 (0.06) | 0.98 | 0.01 (0.07) | 0.84 |
| Trail Making Test, part A[a] | −0.22 (0.48) | 0.64 | 0.44 (0.47) | 0.34 | −0.11 (−0.54) | 0.84 |
| Trail Making Test, part B[a] | −0.53 (0.64) | 0.41 | −0.13 (0.20) | 0.54 | −0.10 (−0.24) | 0.68 |
| HVLT-R learning[b] | 0.26 (0.18) | 0.16 | 0.04 (0.18) | 0.82 | −0.13 (0.21) | 0.53 |
| HVLT-R recall[b] | 0.08 (0.10) | 0.41 | −0.04 (0.10) | 0.70 | −0.05 (0.11) | 0.64 |
| Purdue Pegboard | 0.88 (0.30) | <.0001 | 0.73 (0.31) | 0.02 | 0.64 (−0.35) | <0.07 |
| Brief Test of Attention | −0.27 (0.08) | <.0001 | −0.17 (0.08) | 0.03 | −0.18 (−0.08) | <0.05 |
| Pattern Comparison Test | −0.49 (0.27) | 0.07 | −0.15 (0.25) | 0.56 | −0.43 (−0.29) | 0.14 |
| Clock drawing, command | −0.05 (0.06) | 0.47 | −0.02 (0.06) | 0.75 | −0.04 (−0.08) | 0.56 |
| Clock drawing, copy | 0.02 (0.05) | 0.76 | 0.05 (0.05) | 0.33 | 0.07 (−0.06) | 0.19 |
| Digit Span | −0.30 (0.14) | 0.03 | −0.15 (0.13) | 0.26 | −0.03 (−0.16) | 0.87 |
| Letter fluency | −0.52 (0.33) | 0.12 | −0.32 (0.32) | 0.33 | −0.03 (−0.39) | 0.93 |
| Animal fluency | −0.29 (0.17) | 0.09 | −0.17 (0.17) | 0.31 | −0.15 (−0.19) | 0.44 |

[a] Trail Making Test parts A and B were coded as number of connections per minute, with higher values indicating better performance.

[b] HVLT-R learning and recall were coded as number of items not recalled, with higher values indicating poorer performance.

## Table 3

Cognitive change from baseline to final study visit.

| Outcome | Mean (SD) Initial Visit | Mean (SD) Final Visit | Estimate (SE) | P-value |
|---|---|---|---|---|
| Global Cognition | 28.1 (1.8) | 27.1 (3.3) | 7.0 | <.0001 |
| Trail Making Test, part A[a] | 35.9 (12.8) | 29.8 (12.6) | 8.2 | <.0001 |
| Trail Making Test, part B[a] | 14.0 (5.8) | 10.2 (5.5) | 14.1 | <.0001 |
| HVLT-R learning[b] | 13.2 (5.0) | 14.1 (6.6) | −4.2 | <.0001 |
| HVLT-R recall[b] | 3.8 (2.6) | 4.9 (3.5) | −7.0 | <.0001 |
| Purdue Pegboard | 52.2 (9.6) | 58.0 (15,4) | −8.7 | <.0001 |
| Brief Test of Attention | 6.6 (2.3) | 6.6 (2.4) | 0.7 | 0.49 |
| Pattern Comparison Test | 24.8 (7.2) | 23.2 (7.7) | 6.5 | <.0001 |
| Clock drawing, command | 8.3 (1.7) | 7.8 (1.9) | 3.9 | 0.01 |
| Clock drawing, copy | 9.2 (1.3) | 9.0 (1.4) | 2.7 | <.0001 |
| Digit Span | 13.3 (3.4) | 14.2 (3.7) | −3.1 | 0.002 |
| Letter fluency | 22.0 (8.3) | 14.6 (5.5) | 22.1 | <.0001 |
| Animal fluency | 13.2 (4.3) | 9.4 (3.1) | 17.7 | <.0001 |

[a] Trail Making Test parts A and B were coded as number of connections per minute, with higher values indicating better performance.

[b] HVLT-R learning and recall were coded as number of items not recalled, with higher values indicating poorer performance.