Published in final edited form as:

J Alzheimers Dis. 2017 ; 60(2): 699–706. doi:10.3233/JAD-170287.

Sex-Dependent Associations of Serum Uric Acid with Brain Function During Aging

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Abstract

Serum uric acid (SUA) is an abundant natural antioxidant capable of reducing cellular oxidation, a major cause of neurodegenerative disease. In line with this, SUA levels are lower in Alzheimer's disease; however, the association between SUA and cognition remains unclear. Results from studies examining the effects of SUA on cognition may be difficult to interpret in the context of normal versus pathological aging. This study examined sex-specific associations of baseline SUA with cognition during aging. Data from dementia-free participants initially aged 26–99 ($N=1,451$) recruited for the Baltimore Longitudinal Study of Aging (BLSA), were used in the current analyses. SUA was assessed using blood samples collected during research visits. Cognition was measured using five composite scores (verbal memory, attention, executive function, language, and visuospatial ability). At the first study visit, compared with women, men were older, more likely to be White, had more years of education, higher baseline SUA levels, and higher cardiovascular risk scores. Higher baseline SUA was associated with attenuated declines in attention ($\beta = 0.006$; $p = 0.03$) and visuospatial abilities ($\beta = 0.007$; $p = 0.01$) in men. There was a trend to suggest higher baseline SUA in men was associated with attenuated declines in language, but this finding did not reach statistical significance ($p = 0.09$). There were no significant findings with SUA and cognition in women. In this sample of cognitively healthy, community-dwelling adults, we found that higher SUA levels at baseline were associated with attenuated declines in attention and visuospatial abilities in men. SUA was not associated with cognition or change in cognition over time in women.

Keywords

Aging; cognitive function; older adults; uric acid

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Authors' disclosures available online (<http://j-alz.com/manuscript-disclosures/17-0287r2>).

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-170287>.

INTRODUCTION

Uric acid is a byproduct of purine metabolism and is a powerful antioxidant. Serum uric acid (SUA) is the most abundant natural antioxidant in human plasma. The antioxidant properties of uric acid may reduce the burden of cellular oxidation, a major cause of neurodegenerative diseases [1]. In line with this, previous research shows that SUA levels are lower in those with mild cognitive impairment (MCI), Alzheimer's disease (AD), and vascular dementia when compared with cognitively healthy controls [2–4]. The association between SUA and cognitive performance in middle-aged and older adults remains unclear. Some studies report that higher levels of SUA are associated with poorer cognitive performance [5–12], while others suggest a beneficial effect [13–19]. Accelerated cognitive declines have also been noted in individuals with lower SUA levels [20].

Recent evidence points to the importance of examining sex-specific associations between uric acid and disease outcomes. For instance, higher SUA levels appear to be protective against progression of Parkinson's disease in men, but not women [21]. Other lines of research show that the association between SUA and cardiovascular disease is stronger in women compared to men [22–25]. For instance, a recent meta-analysis found that hyperuricemia had a stronger association with coronary heart disease mortality in women compared to men [25]. In women, there appears to be a dose-response relationship between SUA and stroke risk such that women with higher SUA levels were more likely to be diagnosed with a stroke compared to those with lower levels of SUA [26]. Specific to cognition, a recent study found that among older men, significant increases in SUA were associated with slower declines in attention and processing speed [14].

Results from current studies examining the effects of SUA on cognitive performance may be difficult to interpret in the context of normal versus pathological aging. Indeed, many prior studies on the effects of SUA and cognitive performance [5, 7, 9, 11, 12, 14–16, 18, 19] may have included samples of both normal and cognitively impaired individuals making it difficult to interpret findings. Given these limitations, we sought to explore the association of SUA and cognitive performance in the Baltimore Longitudinal Study of Aging (BLSA) which includes a well-characterized, prospectively followed sample with adjudicated cases of incident dementia. In light of the differential effects of SUA on disease outcomes, the aim in our present study was to examine sex-specific associations of baseline SUA and cognitive performance in BLSA participants free from dementia during follow-up.

METHODS

Sample

The BLSA is a prospective cohort study of community-dwelling adults in Baltimore, MD which began in 1958. Written informed consent was obtained from participants at each visit. The study was approved by the local Institutional Review Board and the National Institute on Aging. Uric acid measurements were available from 2003–2014. Cognitive data was restricted to visits that occurred during 2003–2014. Individuals identifying as race other than

White or Black were excluded due to small sample size (5.8%). Individuals who developed MCI or AD at any point during follow-up were excluded.

Cognitive performance

Five cognitive composite scores were created: verbal memory, attention, executive function, language, and visuospatial ability. Cognitive composite scores were calculated by summing and averaging standardized cognitive measures using the baseline mean and standard deviation. The verbal memory composite was created by using the California Verbal Learning Test [27] immediate free recall and long delay free recall scores. The attention cognitive composite was created by using the Trail Making Test Part A [28] and the Digit Span Forward task [29]. Executive function was defined as the Trail Making Test Part B [28] and the Digit Span Backward task [29]. Language was defined as letter [30] and category [31] fluency. Visuospatial abilities were defined as the Clock 3:25, Clock 11:10 [32], and the Card Rotation [33] tasks. Global cognition was measured using the Mini-Mental State Exam [34].

Measurement of serum uric acid

Blood samples were collected in the morning after a 12-h fast and a 15-min sitting period. Aliquots of serum were obtained and stored at -80°C . Details on uric acid measurement have been previously described [35]. Briefly, uric acid (mg/dL) was measured using an enzymatic-colorimetric method (Bayer, GmbH). The lower limit of detection was 0.2 mg/dL, intra-assay and inter-assay coefficients of variation were equal to 0.5% and 1.7%, respectively.

Covariates

Overall cardiovascular risk was calculated by summing the number of cardiovascular risk factors ascertained by self-reported medical history, physical examination, or laboratory data. These risk factors included hypertension, hypercholesterolemia, diabetes, smoking status, history of angina, myocardial infarction, and transient ischemic attack.

Additional covariates included baseline age, race (White = 1, Black = 0), and years of education. These covariates were chosen based on their clinical and statistical associations with the outcomes of interest (cognitive composite scores).

Sensitivity analysis covariates

Serum uric acid is influenced by dietary factors including animal protein, caffeine and alcohol intake, dairy products, vitamin C, and added sugar [36–42]. In a subset of participants, we had dietary records measured from 2003–2013. Prior to 2005, participants completed a 3-day diet record at home which included two weekdays and one weekend day. However, due to high participant burden and declining compliance, the 3-day diet record was replaced with the self-administered, semi-quantitative food frequency questionnaire (FFQ) which queried participants on their general eating habits for the previous year. Between 2005–2008 there was an overlap period in which participants completed both dietary record measurements. After 2008 participants completed the FFQ. Details regarding methods used to collect dietary data have been detailed previously [43]. Due to disparate

findings between the FFQ and 3-day dietary record and the lack of calibrations made for each nutrient/food group, we only used dietary data collected from the FFQ. Galactose and lactose measurements were averaged to capture dairy product consumption and the total grams of animal protein was derived from the total number of grams of protein.

Linear mixed models analyses

Baseline characteristics of the sample are presented as mean $\pm$ standard deviations and ranges, or frequencies and percentages, and were compared by Student's t-test or chi-squared test, as appropriate. Separate linear mixed effects (LME) models were run with each cognitive composite score as the main outcome and baseline SUA as the main predictor to estimate the association between baseline SUA levels and longitudinal cognitive trajectories in the BLSA. The fixed effects part of the model included: baseline age, race, education, cardiovascular risk score, SUA, and an interaction between time and SUA. The main effect of SUA estimates the baseline crosssectional association between SUA and cognitive performance. The interaction between SUA and time estimates the association between baseline SUA and longitudinal cognitive change. Random effects of the model included intercept and time with unstructured covariance. All cognitive composite scores were standardized with $M = 0$, $SD = 1$. Because of well-known differences in the reference ranges for SUA between men and women [44], all models were stratified by sex.

All analyses were performed using Stata/SE 13.1 (College Station, TX).

RESULTS

Characteristics of the study population at baseline are presented in Table 1. Our sample was 49.7% women and 66.7% white. At first study visit, compared with women, men were older, more likely to be white, have more years of education, higher baseline SUA levels, and higher cardiovascular risk scores. There were no significant differences in number of follow-up years between men and women. As expected, the distribution of baseline SUA differed between the sexes, with men showing higher levels of SUA than women (Supplementary Figure 1). Baseline SUA was relatively stable across age in men and women (Supplementary Table 1). At baseline, 12 women (2%) had SUA values outside of the normal range (i.e., 1.9–7.5mg/dL), whereas 25 men (3%) had SUA values outside of the normal range (i.e., 2.5–8.0mg/dL).

Table 2 displays associations between baseline SUA and cognitive performance based on the linear mixed effects models. Higher baseline SUA was associated with attenuated declines in attention ($\beta = 0.006$; 95% CI 0.0004, 0.01; $p = 0.03$) and visu-ospatial abilities ($\beta = 0.007$; 95% CI 0.001, 0.01; $p = 0.01$) in men. There was a trend to suggest that higher baseline SUA was associated with attenuated declines in language, but it did not reach statistical significance ($\beta = 0.004$, 95% CI -0.001 , 0.009; $p = 0.09$). Higher baseline SUA was associated with lower scores at baseline on the visuospatial abilities composite ($\beta = -0.07$; 95% CI -0.14 , -0.009 ; $p = 0.02$). In women, baseline SUA was not associated with cognitive performance.

Four sensitivity analyses were performed. First, as commonly used diuretics are known to increase SUA levels [45], we performed a sensitivity analysis controlling for the use of diuretics at baseline to determine if these medications had a confounding effect on our key findings. Results remained unchanged after controlling for use of diuretics. Second, we controlled for the effects of drugs used to treat hyperuricemia. In our sample, 31 individuals were using medications to treat hyperuricemia (i.e., Probenecid, Allopurinol). Results remained unchanged after controlling for use of hyperuricemia drugs. Third, in a subset of participants (306 men, 377 women) we had dietary records which characterized macronutrient consumption. As SUA is known to be influenced by the consumption of meat, caffeine, alcohol, dairy products, vitamin C, and sugar [36–42], we performed a sensitivity analyses controlling for dietary factors. First, we examined the association between each dietary factor and SUA. Alcohol, caffeine, and vitamin C were not significantly associated with SUA in our sample whereas greater intake of added sugars and animal protein was associated with higher SUA levels and greater intake of dairy products was associated with significantly lower SUA levels. Second, we used LME models with each dietary factor (i.e., animal protein, dairy products, and added sugar) along with an interaction term with dietary factor and SUA to determine if diet affected the relationship between SUA and cognition. Several differences in our key findings emerged (Supplementary Tables 2–4). After controlling for the consumption of animal protein, there were significant cross-sectional findings in women. Higher baseline SUA was associated with poorer performance on measures of visuospatial abilities ($\beta = -0.14$; 95% CI $-0.28, -0.002$; $p = 0.04$) and language ($\beta = -0.12$; 95% CI $-0.23, -0.01$; $p = 0.02$; Supplementary Table 2). In men, the significant findings associated with attenuated declines in attention and visuospatial abilities remained the same, but there was a trend to suggest that higher baseline SUA was also associated with attenuated declines in verbal memory ($\beta = 0.009$; 95% CI $-0.001, 0.02$; $p = 0.08$). When controlling for dairy products, there was a non-significant trend in men to suggest that higher baseline SUA was associated with attenuated declines in attention ($\beta = 0.15$; 95% CI: $-0.01, 0.32$; $p = 0.07$; Supplementary Table 3), but all other associations between SUA and cognitive performance were nonsignificant. When examining the effects of added sugar on the relationship between baseline SUA and cognitive performance (Supplementary Table 4), we find a non-significant trend to suggest that higher baseline SUA is associated with attenuated declines on the Mini-Mental State Exam in women ($\beta = 0.21$, 95% CI: $-0.03, 0.45$, $p = 0.09$) and attenuated declines in attention in men ($\beta = 0.16$; 95% CI: $-0.01, 0.33$; $p = 0.07$). Lastly, we looked at age effects on the association between SUA and cognition. Our sample includes relatively young adults who are unlikely to contribute to the true trajectory of cognitive decline with aging. In our fourth sensitivity analysis, we restricted the sample to those aged 50 and older. Results remained unchanged after excluding younger participants.

DISCUSSION

In this sample of cognitively healthy, communitydwelling middle-aged and older adults, we found that higher SUA levels at baseline were associated with attenuated declines in cognitive performance in men. These findings are consistent with previous reports that higher levels of SUA are protective against cognitive decline [13]. Using data from the

Women's Health and Aging Study, Vannorsdall and colleagues reported that higher baseline SUA was cross-sectionally associated with poorer working memory performance and a trend toward slower manual speed. Consistent with findings from the Women's Health and Aging Study [5], we found no longitudinal associations of serum uric acid with verbal memory or executive function in women. Results from the Rotterdam study suggest that higher SUA levels at baseline were associated with a decreased risk of dementia and better performance on measures of global cognitive function, executive function, and memory only after controlling for cardiovascular risk factors [13] which is in line with our findings. Sex-dependent effects of SUA on cognitive performance were reported in the ELSA-Brazil cohort study, a middle-aged sample of civil servants. Higher SUA at baseline was associated with better performance on a measure of executive function, the Trail Making Test Part B, in men, but not women. There were no significant effects of SUA on measures of verbal fluency or memory [46]. Contrary to our results, Schretlen et al. [7] reported an association between higher levels of uric acid and impaired memory performance in 96 community-dwelling participants. However, given the small sample size and the limited number of cardiovascular risk factors adjusted for in the analyses, it may have been difficult to discern the contradictory properties of uric acid in relation to cognitive performance in this sample.

The relationship between SUA and cognitive performance in our study was dependent upon several factors including the cognitive domain measured and sex. Specifically, we found a beneficial effect of higher baseline SUA levels on changes in cognitive performance in the domains of attention and visu-ospacial abilities in men, but no effects in women. Diet also appears to influence the association between SUA and cognitive performance in a subset of BLSA participants. It should be noted that dietary data was available only for a subset of the original sample and only measured over a 5-year period (2008–2013). This relatively short follow-up period would make it more difficult to observe longitudinal changes in cognitive performance associated with baseline SUA. Individuals with dietary data were more likely to be older and report more cardiovascular risk factors than those without dietary data. Men with dietary data were on average eight years older than those without ($M = 73.9$ years with dietary data; $M = 65.8$ years without dietary data; $p < 0.0001$) whereas women with dietary data were on average 10 years older than those without dietary data ($M = 72.3$ years with dietary data; $M = 62.5$ years without dietary data; $p < 0.0001$). BLSA participants follow a healthier diet compared to the general population. When compared to participants from the National Health and Nutrition Examination Survey (NHANES, 2005–2006, 2007–2008), BLSA participants consumed less calories, more dietary fiber, and had higher levels of macronutrient intake including alpha carotene, beta carotene, and vitamins C and K [43]. The consumption of animal protein appears to influence the relationship between SUA and cognitive performance in women. After controlling for animal protein, we found that higher baseline SUA was associated with poorer performance in visuospatial abilities and language in women at baseline.

Research suggests that there are sex-dependent effects in the association between the urate transporter gene, SLC2A9 and SUA levels [47]. It is interesting that higher levels of SUA were associated with cognitive performance only in men in our sample. Genetic factors may explain the role of SUA in cognitive performance. Serum uric acid levels are highly heritable and several genome-wide associations studies have identified single nucleotide

polymorphisms (SNPs) that are strongly associated with uric acid levels [48–50]. Variations in the SLC2A9 gene have been shown to influence serum uric acid levels [51]. In the kidneys, the physiological role of SLC2A9 is the reabsorption of urate from urine into the blood which can increase levels of SUA when SLC2A9 expression is upregulated [51]. Polymorphisms in the SLC2A9 gene have been associated with cognition. In the Lothian Birth Cohort 1936 study, SLC2A9 SNPs associated with an increase in uric acid were also associated with better performance on memory-related tasks [52]. This may explain the sex-dependent effects of uric acid found in our study, but the underlying mechanisms should be further investigated.

The sometimes inconsistent findings between serum uric acid levels and cognition may be due to both its antioxidant function in plasma and its prooxidant properties in neurons [1]. Elevations in SUA may reduce cellular oxidation that is seen in many neurodegenerative diseases like Parkinson's disease [21, 53] and AD [3, 54]; whereas the deleterious effects of uric acid may be due in part to its associations with an increased risk of a number of diseases known to impact cognitive performance [7, 12, 26, 55]. *In vivo*, naturally created and ingested purines are metabolized by xanthine oxidase to xanthine and then to uric acid. This process results in the creation of free radicals which can add to the oxidative stress burden. So, while SUA is itself an antioxidant, its creation *in vivo* may contribute to oxidative stress [56].

Our study has several strengths. Our sample has over ten years of follow-up data and a rich battery of cognitive tests in multiple cognitive domains. Our prospective cohort design with adjudicated cases of dementia allowed us to ensure that participants in these analyses were free from dementia and cognitive impairment (e.g., MCI) at baseline and during the follow-up period. This gives us a better understanding of the role of SUA in normal cognitive aging. SUA is known to be influenced by diet, especially meat consumption, added sugars, and dairy products [36–42]. Using dietary records, we were able to control for these dietary factors. Despite the strengths of our study, a few limitations must be noted. First, residual confounding cannot be ruled out because this was not a randomized, controlled study. Second, due to a small number of Non-White or Non-Black minority participants (5.8%), we were unable to include these participants in our current analyses. The relationship between SUA and cognitive performance may differ in other ethnic minority groups. Finally, understanding whether SUA levels may exert regionally specific effects in the brain and whether such effects differ by sex may require additional studies in relevant experimental model systems. Such studies may be essential to understand the mechanisms underlying domain-specific effects on cognitive performance observed in men in our study. In conclusion, higher baseline levels of SUA were associated with attenuated declines in attention and visuospatial abilities in men. Thus, higher SUA levels appear to be protective against future cognitive decline in middle-aged and older adult men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors are grateful to the Baltimore Longitudinal Study of Aging participants and staff for their dedication to these studies. This work was supported entirely by the Intramural Research Program of the National Institute of Health (NIH), National Institute on Aging (NIA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

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Table 1

Demographic characteristics by sex

	Men (<i>n</i> = 729)	Women (<i>n</i> = 722)	<i>p</i> -value
Age at first visit, M ± SD, range	65.8 ± 14.1, 27–96	62.5 ± 13.7, 26–99	<0.0001
White, <i>n</i> (%)	525 (72.0)	443 (61.3)	<0.0001
Years of education, M ± SD, range	17.1 ± 2.6, 0–30	16.7 ± 2.5, 8–24	0.002
Baseline serum uric acid (mg/dL), M ± SD, range	5.70 ± 1.27, 3.1–11.5	4.55 ± 1.33, 2.4–8.6	<0.0001
Cardiovascular risk score M ± SD, range	1.26 ± 1.10, 0–6	0.89 ± 0.84, 0–4	<0.0001
Animal protein in grams, M ± SD, range	56.9 ± 29.2, 0–161.9	49.9 ± 28.9, 0–247.8	<0.0001
Number of visits, M ± SD, range	2.5 ± 1.7, 1–11	2.4 ± 1.6, 1–11	0.036
Follow-up time in years, M ± SD, range			
Mini-Mental State Exam	3.5 ± 3.2, 0–11.9	3.8 ± 3.3, 0–11.8	0.87
Memory	3.3 ± 3.2, 0–11.7	3.5 ± 3.3, 0–11.7	0.89
Attention	3.2 ± 3.1, 0–11.6	3.1 ± 3.1, 0–11.6	0.99
Executive function	3.1 ± 3.0, 0–11.3	3.1 ± 3.1, 0–11.6	0.96
Visuospatial abilities	3.0 ± 3.0, 0–11.3	3.0 ± 3.0, 0–11.6	0.99
Language	3.2 ± 3.1, 0–11.9	3.3 ± 3.2, 0–11.8	0.99

Table 2

Associations of baseline serum uric acid with cognitive performance by sex

	Men			Women		
	β^*	(95% CI)	<i>p</i> -value	β^*	(95% CI)	<i>p</i> -value
Mini-Mental State Exam						
Intercept	0.02	(-0.06, 0.08)	0.69	0.02	(-0.11, 0.16)	0.73
Slope	-0.002	(-0.01, 0.01)	0.56	-0.004	(-0.01, 0.01)	0.52
Verbal Memory						
Intercept	-0.01	(-0.10, 0.07)	0.77	-0.004	(-0.09, 0.08)	0.92
Slope	0.003	(-0.003, 0.01)	0.35	-0.002	(-0.01, 0.004)	0.46
Attention						
Intercept	-0.02	(-0.09, 0.04)	0.46	-0.002	(-0.07, 0.06)	0.94
Slope	0.006	(0.0004, 0.01)	0.03	-0.0002	(-0.006, 0.005)	0.94
Executive function						
Intercept	0.02	(-0.05, 0.09)	0.57	0.02	(-0.05, 0.10)	0.56
Slope	0.001	(-0.004, 0.007)	0.60	-0.002	(-0.009, 0.004)	0.44
Visuospatial						
Intercept	-0.07	(-0.14, -0.009)	0.02	-0.03	(-0.10, 0.03)	0.35
Slope	0.007	(0.001, 0.01)	0.01	-0.001	(-0.007, 0.01)	0.83
Language						
Intercept	-0.03	(-0.09, 0.03)	0.34	-0.01	(-0.07, 0.04)	0.68
Slope	0.004	(-0.001, 0.009)	0.09	-0.001	(-0.006, 0.004)	0.80

* Beta coefficients are adjusted for age, race, years of education, and cardiovascular risk score. Cognitive scores are standardized with M = 0, SD = 1.