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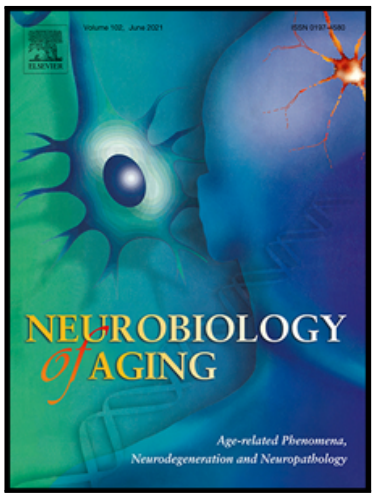

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Highlights

- Contrasting role for serum uric acid between normal cognition and AD.
- The effect of serum uric acid on cognitive decline was observed only in female MCI patients.
- The observed effects for uric acid differed according to the presence of *APOE4*.
- Serum uric acid exerted beneficial effects on cognitive decline that were mediated by brain metabolism.

Effects of baseline serum uric acid and apolipoprotein E4 on longitudinal cognition and cerebral metabolism

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Abstract

Serum uric acid, a natural antioxidant, may have a protective effect on the progression of Alzheimer's disease (AD). To investigate the effect of serum uric acid on longitudinal cognitive and brain metabolic changes, we utilized data on baseline serum uric acid levels, *APOE* genotyping, and longitudinal cognitive scores from the Alzheimer's Disease Neuroimaging Initiative for 1,343 participants with normal cognition (NC), mild cognitive impairment (MCI), or dementia. In 979 participants, brain metabolism was measured using

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) images. Higher serum uric acid levels exhibited a detrimental effect on NC, whereas a protective trend was observed in individuals with cognitive impairment. Interestingly, higher uric acid levels were associated with a slower decline in cognitive scores and brain metabolism in females with MCI, and this effect was found in *APOE4* carriers, but not in non-carriers. Longitudinal AD-like patterns of brain metabolism on FDG-PET images also appeared to mediate the effects of baseline uric acid levels on longitudinal cognitive decline. In summary, higher serum uric acid may interact with *APOE4* to alleviate longitudinal metabolic changes and cognitive decline in female MCI patients.

Keywords: Alzheimer's disease, serum uric acid, cognition, brain metabolism, apolipoprotein E4.

1. Introduction

Alzheimer's disease (AD) is the leading cause of neurodegenerative dementia and is characterized by cerebral accumulation of beta amyloid (Aβ) (Masters et al., 1985). According to the amyloid cascade hypothesis, cerebral Aβ deposition precedes and induces the spread of pathologic tau, synaptic or neuronal degeneration, and cognitive dysfunction (Jack et al., 2018). Cerebral Aβ deposition can be identified using cerebrospinal fluid (CSF) Aβ (Hansson et al., 2018) and amyloid positron emission tomography (PET) (Clark et al., 2012), while synaptic degeneration can be assessed using ^{18}F-fluorodeoxyglucose PET (FDG-PET) (Dubois et al., 2007; Ou et al., 2019). Combining abnormal amyloid biomarkers with FDG-PET provides powerful prediction of cognitive decline (Jack et al., 2018), and synaptic degeneration is one of the best neural correlates of the clinical features of AD (DeKosky and Scheff, 1990; Terry et al., 1991).

An increasing body of evidence suggests that oxidative stress is closely related to synaptic dysfunction and disease progression in degenerative diseases, including AD (Ansari and Scheff, 2010; Mosconi et al., 2008) and Parkinson's disease (PD) (Schirinzi et al., 2020). Meanwhile, previous studies have shown that lower serum uric acid levels are associated with a higher risk of degenerative dementias, including AD, PD, and tauopathies (Schirinzi et al., 2017; Zhou et al., 2021). Research has also indicated that higher serum uric acid levels are associated with a lower risk of developing dementia and better cognitive function in non-demented older adults (Du et al., 2016; Euser et al., 2009; Wang et al., 2017; Wu et al., 2013) and that gout, characterized by excess serum uric acid, is inversely associated with the risk of developing AD (Hong et al., 2015; Lu et al., 2016). Accordingly, uric acid, a natural antioxidant, (Ames et al., 1981; Bowman et al., 2010) could offer protective effects against cognitive decline. Indeed, in our previous study using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we discovered that higher serum uric acid levels alleviated

the detrimental effects of CSF Aβ (Ye et al., 2016).

Apolipoprotein E4 *(APOE4)* is an important genetic risk factor in AD, primarily in Aβ-dependent mechanisms. However, previous studies have also suggested that, as an Aβ-independent mechanism, *APOE4* is associated with higher oxidative stress and lower antioxidant defense in patients with AD (Cioffi et al., 2019; Kharrazi et al., 2008; Miyata and Smith, 1996; Ramassamy et al., 1999; Tamaoka et al., 2000). Others have shown that oxidative stress is closely related to synaptic dysfunction and brain hypometabolism on FDG-PET (Mosconi et al., 2008). Therefore, the effects of serum uric acid on cognitive dysfunction and the risk of AD could be influenced by *APOE4* through mediation of oxidative stress reflected in brain metabolism on FDG-PET images.

This study aimed to investigate the effect of baseline serum uric acid in relation to *APOE4* on longitudinal cognitive and metabolic changes using data from the ADNI. Since oxidative stress is increased in mild cognitive impairment (MCI) and AD dementia patients (Schrag et al., 2013) and since the protective effects of estrogen against oxidative stress disappear in older female adults (Kander et al., 2017), we hypothesized that the effect of serum uric acid could differ according to cognitive status, gender, and the presence of *APOE4*.

2. Materials and Methods

2.1 Participants and baseline characteristics

Data were obtained from the ADNI database (http://adni.loni.usc.edu/). The ADNI is a longitudinal study launched in 2003 as a public-private partnership. The goal of the ADNI has been to determine whether serial magnetic resonance imaging, PET, CSF and blood biomarkers, and clinical and neuropsychological assessment can be combined to assess progression of MCI and early AD.

The inclusion and exclusion criteria for subjects in the ADNI database are provided at the ADNI website (http://adni.loni.usc.edu/methods/documents/). Briefly, diagnosis of dementia was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 1984). Abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale, a Mini-Mental State Examination (MMSE) score between 20 and 26 (inclusive), and a Clinical Dementia Rating (CDR) score of 0.5 to 1 are required for diagnosis of AD. Individuals with MCI had preserved general cognition and functional performance and were required to have abnormal memory function, a MMSE score between 24 and 30, and a CDR score of 0.5. Impairment of instrumental activities in daily living were qualitatively judged by site investigators without cut-off on a specific test.

In this study, 1,343 individuals with available information on baseline serum uric acid levels, *APOE* genotype, and longitudinal neuropsychological assessment results were selected. As the diagnosis of gout could modify the risk of cognitive impairment (Hong et al., 2015; Lu et al., 2016), patients with gout diagnosis and those who were treated with medication for gout were excluded. Baseline characteristics, including demographics, smoking status, body mass index (BMI), and medical history were recorded. Estimated

glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation (Levey et al., 2006).

2.2 Standard protocol approvals, registrations, and patient consents

According to ADNI protocols, all procedures performed in studies involving human participants were conducted in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants. More details can be found at adni.loni.ucs.edu.

2.3 Vascular risk factors

The following search terms were used to select those with a medical history of (1) diabetes mellitus: diabetes, diabetic, and insulins; (2) hypertension: hypertension, HTN, high blood pressure, high BP, elevated BP, increased blood pressure, and elevated blood pressure; (3) atrial fibrillation: atrial fibrillation, A-fib, A fib, atrial fib, and afib; (4) stroke: stroke, ischemic stroke, transient ischemic attack, TIA, cerebrovascular disease, and CVA; (5) dyslipidemia: dyslipidemia, hyperlipidemia, hypercholesterolemia, high cholesterol, elevated cholesterol, and increased cholesterol; (6) cardiovascular disease: myocardial infarction, MI, coronary artery disease, and CAD. Each vascular risk factor was treated as a dichotomized value.

2.4 Neuropsychological assessment

General cognitive function at baseline and follow-up time points was measured using the MMSE. Composite scores for executive (Gibbons et al., 2012), memory (Crane et al., 2012), language, and visuospatial functions were available in the UWNPSYCHSUM file from the

ADNI website (update date: 03-26-2020).

2.5 FDG-PET evaluation

Among 1,343 participants, brain metabolism on FDG-PET was measured longitudinally in 979 participants. Each image scan was spatially normalized to the Statistical Parametric Mapping template and analyzed using voxel-based image protocols. A global index for FDG-PET was summarized as the hypometabolic convergence index (HCI), which was designed to reflect AD-like patterns and magnitudes of brain metabolism (Chen et al., 2011). HCI values for the participants were provided in the BAIPETNMRCFDG file (update date: 11-22-2019) from the ADNI website. FDG-PET measurements of a set of pre-defined regions of interest, including the bilateral angular gyrus, bilateral inferior temporal gyrus, and bilateral posterior cingulum, were also available in the UCBERKELEYFDG file from the ADNI website (update date: 05-28-2020) (Landau et al., 2011).

2.6 Aβ positivity

A subset of the participants underwent baseline CSF Aβ measurement using INNO-BIA AlzBio3 assay. A CSF Aβ level <192 was considered Aβ positive (Shaw et al., 2009). Cortical florbetapir standardized uptake value ratio (SUVR) was calculated by averaging four cortical regions, including the frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal areas, divided by the whole cerebellum reference region. The values for the participants were available in the UCBERKELEYAV45 file from the ADNI website (update date: 05-12-2020). A florbetapir SUVR >1.11 was considered Aβ positive (Joshi et al., 2012). Only baseline CSF Aβ and florbetapir PET measurements were used to assess Aβ positivity.

2.7 Statistical analysis

Statistical analyses of the demographic, clinical, and brain metabolism data were performed using IBM Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA). Analyses of variance and chi-square tests were used to compare demographic variables.

To evaluate the effects of baseline serum uric acid on cognitive scores and FDG-PET measurements, we used linear mixed models with the interaction between baseline serum uric acid and year (follow-up years from baseline) as a predictor (Model 1). Covariates included age, education, *APOE4* status (*APOE4* carrier vs. non-carrier), BMI, eGFR, vascular risk factors, year, and baseline serum uric acid. As the normal range of serum uric acid levels differed by sex, all analyses were conducted separately for female and male participants.

To investigate whether the effects of serum uric acid on cognitive scores and FDG-PET measurements differed according to the presence of *APOE4*, we used linear mixed models with the interaction between baseline serum uric acid and year (serum uric acid*year), *APOE4* and year (APOE4*year), and three-way interactions between baseline serum uric acid, APOE4, and year (baseline serum uric acid**APOE4**year) as predictors (Model 2). Covariates included age, education, BMI, eGFR, vascular risk factors, year, baseline serum uric acid, and baseline serum uric acid**APOE4*. Additionally, subgroup linear mixed models for longitudinal cognitive scores and FDG-PET measurements were separately performed for *APOE4* carrier and non-carrier subgroups using baseline serum uric acid*year as a predictor. Covariates included age, education, BMI, eGFR, vascular risk factors, year, and baseline serum uric acid (Model 3).

To analyze whether the effects of baseline serum uric acid on longitudinal cognitive scores depend on its effects on longitudinal FDG-PET measures, we further included HCI at each time point as a predictor in addition to baseline serum uric acid*year in linear mixed models 1 and 3. Sensitivity analyses for linear mixed models 1, 2, and 3 were conducted after

further controlling for baseline Aβ positivity as a covariate.

2.8 Data availability

All data generated or analyzed during this study can be obtained via the ADNI website (http://adni.loni.usc.edu/).

3. Results

3.1 Demographic and clinical characteristics

There were no significant differences in terms of hypertension, stroke, atrial fibrillation, and *APOE4* status between the female and male participants (Table 1). The male participants were older and had higher education, BMI, eGFR, and baseline serum uric acid levels than the female participants. The proportions of participants with smoking history, diabetes mellitus, dyslipidemia, and cardiovascular disease were higher in the male group than in the female group. Baseline memory composite scores were higher in the female group than in the male group. In terms of baseline FDG-PET measurements, the female group showed higher baseline brain metabolism in the bilateral angular and left temporal gyri than the male group. The male group had higher baseline HCI values than the female group, suggesting more AD-like hypometabolism. When the participants were classified according to baseline cognitive status, duration of follow-up, MMSE, cognitive scores, brain metabolism differed between NC, MCI, and dementia groups (Supplementary Table 1).

3.2 Effects of baseline serum uric acid on longitudinal cognition and brain metabolism

Linear mixed model 1 showed that the effects of baseline serum uric acid on longitudinal cognitive scores were not significant in either the female or male group (Table 2). When participants were categorized according to baseline cognitive status, baseline serum uric acid*year was significantly associated with lower MMSE scores in the female NC and male NC subgroups. Baseline serum uric acid*year was associated with higher MMSE and cognitive scores in the memory, executive, and language domains in the female MCI subgroup. However, the effect of baseline serum uric acid*year was not significant in the male MCI, female dementia, and male dementia subgroups.

Linear mixed model 1 showed that the effects of baseline serum uric acid on

longitudinal brain metabolism were not significant in either the female or male group (Table 3). However, when participants were categorized according to baseline cognitive status, baseline serum uric acid*year was significantly associated with higher left temporal gyrus metabolism and lower HCI in the female MCI subgroup. However, it was not associated with brain metabolism in other subgroups.

3.3 Interaction between baseline serum uric acid and *APOE4* on longitudinal cognition and brain metabolism

In the female MCI subgroup, linear mixed model 2 for longitudinal cognitive scores and brain metabolism using baseline serum uric acid*year, *APOE4**year, and baseline serum uric acid**APOE4**year as predictors showed that baseline serum uric acid**APOE4**year significantly affected MMSE scores, cognitive scores of the language and visuospatial domains, and HCI (Table 4). *APOE4**year was associated with lower MMSE scores, lower cognitive scores of executive, language, and visuospatial domains, and lower metabolism in the bilateral angular and temporal gyri and higher HCI. However, the baseline serum uric acid*year effect was not significant.

3.4 Subgroup analyses for the effects of baseline serum uric acid on longitudinal cognition and brain metabolism in female MCI patients with and without *APOE4*

In female MCI patients with *APOE4*, the linear mixed model 3 for longitudinal cognitive scores showed that baseline serum uric acid*year was associated with higher MMSE and cognitive scores of the executive, language, and visuospatial domains (Supplementary Table 2). In female MCI patients without *APOE4*, baseline serum uric acid*year was associated with higher cognitive score in the executive domain, but not in other domains.

The linear mixed model 3 for longitudinal brain metabolism for female MCI patients

with *APOE4* showed that baseline serum uric acid*year was associated with lower HCI and higher metabolism in the bilateral angular gyri, left temporal gyrus, and bilateral cingulum. In female MCI patients without *APOE4*, the baseline serum uric acid*year effect was not significant.

3.5 Effects of baseline serum uric acid on longitudinal cognitive scores with and without consideration for HCI in female MCI patients with *APOE4*

To determine whether the effects of baseline serum uric acid on longitudinal cognition depended on AD-like metabolic changes, we included HCI values at each time point as a predictor in addition to the baseline serum uric acid*year in Models 1 and 3, respectively. The updated models in the female MCI subgroup showed that the observed effects for baseline uric acid*year on MMSE and cognitive scores in the memory, executive, and language domains, which were significant in Model 1 (Table 2), were no longer significant, whereas the effects of HCI were significant for all cognitive scores (Table 5). Additionally, the updated models in the female MCI with *APOE4* subgroup showed that the baseline uric acid*year effects on MMSE and cognitive scores in the executive, language, and visuospatial domains, which were significant in Model 3 (Supplementary Table 2), were no longer significant, whereas the effects of HCI were significant for all cognitive scores (Table 5).

3.6 Sensitivity analyses after further controlling for Aβ positivity

To explore the possibility that Aβ positivity confounded the associations between uric acid, *APOE4*, cognitive dysfunction, and cerebral metabolism, sensitivity analyses were conducted after further controlling for baseline Aβ positivity. Model 1 sensitivity analyses for cognitive scores showed results similar to that of the original analyses without controlling for Aβ positivity, except that the baseline serum uric acid*year was additionally associated with a

higher visuospatial composite score in the female MCI subgroup and higher MMSE score in the female dementia subgroup (Supplementary Table 3). Model 1 sensitivity analyses for FDG-PET measures also showed results similar to that in the original analyses, except that the baseline serum uric acid*year was additionally associated with lower HCI in the female group and higher right temporal metabolism in the female MCI subgroup (Supplementary Table 4). Model 2 sensitivity analyses further controlled for Aβ positivity in the female MCI subgroup showed that the baseline serum uric acid**APOE4**year effect was not significantly associated with language composite scores and HCI (Supplementary Table 5), which was significant in the original model (Table 4). However, Model 3 sensitivity analyses separately performed in female MCI *APOE4* carriers and non-carriers showed results similar to that in the original analyses (Supplementary Table 2), except that the baseline serum uric acid*year effect was additionally associated with higher metabolism in the right temporal gyrus (Supplementary Table 6). Sensitivity analyses for the independent effects of baseline serum uric acid*year and HCI on longitudinal cognition showed results similar to that in the original analyses (Table 5), except that the baseline uric acid*year effects remained significantly associated with MMSE and executive composite scores even after controlling for HCI (Supplementary Table 7).

4. DISCUSSION

In this study, we evaluated the effect of serum uric acid on longitudinal cognition and brain metabolism in the overall cognitive status from normal aging to dementia using the ADNI dataset. The major findings of our study are as follows. First, higher serum uric acid levels were associated with faster general cognitive decline in NC participants, while it tended to be associated with slower cognitive decline in MCI and dementia patients. Second, beneficial effects for uric acid on longitudinal cognitive and metabolic decline were observed only in female MCI patients. Third, the effect of serum uric acid on longitudinal cognitive and metabolic decline differed according to the presence of the *APOE4* allele in that the beneficial effect was observed only in *APOE4* carriers. Fourth, serum uric acid had beneficial effects on longitudinal cognitive decline with the mediation of brain metabolism. Taken together, our results suggest that higher serum uric acid interacts with *APOE4* to slow down cerebral metabolic and cognitive decline in female MCI patients, whose vulnerability to oxidative stress could be important in AD progression.

The direction of baseline serum uric acid effects on cognitive decline differed in NC subjects and in MCI/dementia patients. Higher baseline serum uric acid levels were associated with a faster MMSE decline in NC participants. Although a statistical significance was not attained, Table 2 shows that the direction of beta coefficients in the MCI and dementia patients was the opposite of that in the NC participants. These results could be related to increased oxidative stress in MCI and AD dementia patients (Schrag et al., 2013), but not in NC participants. In NC participants without significant oxidative stress, higher levels of serum uric acid could be associated with an increased risk of cerebrovascular disease (Lehto et al., 1998) and an increased burden of cerebral white matter hyperintensities (WMHs), leading to cognitive dysfunction (Schretlen et al., 2007; Vannorsdall et al., 2008). This point of view is further supported by previous studies showing that higher serum uric

acid levels are associated with an increased risk of developing vascular dementia, but not AD, in older individuals (Latourte et al., 2018). Although both MCI and AD dementia patients have an increased oxidative stress burden (Schrag et al., 2013), our results suggest that the effect of oxidative stress on cognitive decline could be more prominent in the MCI stage than in the dementia stage.

Consistent with our hypothesis, only female MCI patients showed a significant relationship between higher serum uric acid levels and slower cognitive decline. This result suggests that cognitive vulnerability to oxidative stress may differ according to sex. After menopause, females become more vulnerable to oxidative stress with the disappearance of protective estrogen effects against oxidative stress (Kander et al., 2017). However, a previous study performed in patients with PD showed that higher serum uric acid levels were associated with better white matter integrity only in males (Lee et al., 2020). Considering that AD (Pike, 2017) and PD (Cerri et al., 2019) have female and male preponderance, respectively and that oxidative stress also plays an important role in the pathogenesis of PD (Jenner, 2003; Schirinzi et al., 2020), there could be a significant interaction between sex and the type of pathogenic protein (Aβ or tau vs. α-synuclein) in terms of vulnerability to oxidative stress. On the other hand, there is another possibility that cerebrovascular disease could have confounded the relationship between uric acid and cognitive decline in males. Since males have a higher risk of cerebrovascular disease than females (Appelros et al., 2009), higher cerebrovascular burden associated with higher serum uric acid could have counteracted the antioxidant effects of uric acid. Although the participants in the ADNI had minimal vascular components at baseline, because mild WMH was required during enrollment (Ramirez et al., 2016), future studies considering longitudinal changes in WMH are required to exclude the confounding effects of cerebrovascular burden.

The effects of baseline serum uric acid in female MCI patients differed according to

the presence of the *APOE4* allele. This significant interaction between serum uric acid and *APOE4* suggests that the antioxidant effect of higher serum uric acid levels could be especially important in *APOE4* carriers who have high oxidative stress and low antioxidant defense (Cioffi et al., 2019; Kharrazi et al., 2008; Miyata and Smith, 1996; Ramassamy et al., 1999; Tamaoka et al., 2000). This is supported by previous studies. In an animal model study, the brains of female mice with human *APOE4* had higher oxidative stress, which mostly accumulated in the synaptic terminals (Shi et al., 2014). Human RNAseq-based analysis also demonstrated that genes related to oxidative stress are highly expressed in female *APOE4* carriers (Hsu et al., 2019). However, considering that *APOE4* is the most important genetic risk factor for sporadic AD, there is another possibility that cognitively impaired patients with pathologies other than AD, such as vascular cognitive impairment or Lewy body disease, were included in the *APOE4* non-carrier MCI group, rather than another group. If patients with higher serum uric acid levels had smaller degrees of AD pathology, the most important contributor of longitudinal cognitive decline, then slower metabolic and cognitive decline could be explained. However, this hypothesis is less likely because our sensitivity analyses further controlling for Aβ positivity (Supplementary Table 6) showed results similar to that of the original analyses (Supplementary Table 2). Although Model 2 sensitivity analyses further controlled for Aβ positivity in the female MCI subgroup showed that baseline serum uric acid**APOE4**year effect was not significantly associated with HCI (Supplementary Table 5), which was significant in the original model (Table 4), this could be due to the smaller sample size of individuals with data available on Aβ positivity.

The beneficial effects of higher serum uric acid levels on longitudinal cognitive decline in female MCI patients disappeared after controlling for HCI at each time point. This result suggests that the protective effect of serum uric acid on cognition is mediated by AD-related hypometabolism. Corroborating this point of view, a previous cross-sectional study

showed that lower serum uric acid is associated with AD-related hypometabolism among non-demented older individuals, which in turn correlates with memory dysfunction (Kim et al., 2020). Previous studies have shown that serum uric acid is not directly associated with Aβ and tau burden on PET (Kim et al., 2020) or in CSF (Ye et al., 2016) and that higher serum uric acid could be a protective factor slowing cerebral metabolic decline with a given amount of Aβ and tau pathologies. Our results suggest that cerebral metabolic changes on FDG-PET, which is an upstream event of cognitive dysfunction in AD (Sperling et al., 2011), successfully reflected the antioxidant effects of uric acid in *APOE4* carriers with exacerbated oxidative stress (Drzezga et al., 2005; Verghese et al., 2011). The antioxidant effects of higher serum uric acid could dissociate the degree of synaptic dysfunction (Ansari and Scheff, 2010; Mosconi et al., 2008) from the burden of AD pathologies. However, as sensitivity analyses further controlled for Aβ positivity showed that baseline serum uric acid had significant effects on longitudinal changes in MMSE and executive composite scores even after controlling for HCI (Supplementary Table 7), there could be other mechanisms supporting the beneficial effects of uric acid on cognitive decline, including AD-unrelated metabolic changes.

Our study has several limitations. First, we could not include WMH analysis in this study. Although we controlled for various cardiovascular and cerebrovascular risk factors, direct measurement of vascular burden in the brain is required for a comprehensive explanation of the role of serum uric acid. Second, although we observed an association between serum uric acid levels and longitudinal cognitive and metabolic changes, a causal relationship between uric acid and cognition is not guaranteed. Additionally, lower BMI and lower uric acid could reflect poor nutritional status in patients with deteriorating cognition (Faxén-Irving et al., 2014). Although we included BMI as a covariate in our analyses, our results should be interpreted cautiously. Third, although we controlled for the baseline

demographics as covariates in our statistical analyses separately in male and female subjects, some demographic variables including age, education, vascular risk factors, BMI, and eGFR were significantly different between female and male groups. Fourth, Aβ status was not evaluated in all of the study participants. Considering the close relationship between Aβ and *APOE4*, Aβ could confound the relationship between serum uric acid and *APOE4*. However, our sensitivity analyses including Aβ positivity as a confounding factor showed similar results to those in the original analyses.

In conclusion, female MCI patients exhibited protective effects of higher serum uric levels on longitudinal declines in cognition and brain metabolism. It is possible that serum uric acid, as a natural antioxidant, is protective only in individuals with the highest degrees of oxidative stress, whereas it could be harmful in those with normal cognition. Our findings suggest that antioxidative strategies should be emphasized as a therapeutic strategy in a selected group of cognitively impaired patients due to AD, especially in female patients with MCI and with *APOE4*.

Credit author statement

Study concept and design: Lee and Ye.

Acquisition, analysis, or interpretation of the data: Lee and Ye.

Drafting of the manuscript: Lee and Ye.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Lee and Ye.

Study supervision: Ye.

Declaration of Competing Interest

None

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Figures

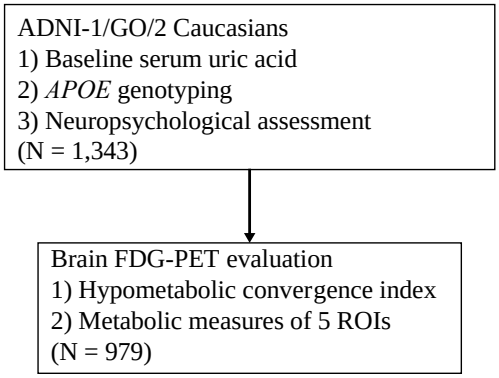

Figure 1. Flowchart of the study participants.

Abbreviations: ADNI, Alzheimer Disease Neuroimaging Initiative; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ROI, region of interest.

Tables

Table 1. Baseline demographics and clinical characteristics

	Total	Female	Male	*P* value
Number	1,343	603	740	
Age, year	73.9 (7.2)	73.0 (7.2)	74.6 (7.0)	< **0.001**
Education, year	15.9 (2.8)	15.3 (2.7)	16.4 (2.8)	< **0.001**
Baseline diagnosis				**0.014**
Normal cognition	360 (26.8)	183 (30.4)	177 (23.9)	
MCI	724 (53.9)	301 (49.9)	423 (57.2)	
Dementia	259 (19.3)	119 (19.7)	140 (18.9)	
Vascular risk factors				
Hypertension	588 (43.8)	248 (41.1)	340 (45.9)	0.077
Diabetes mellitus	94 (7.0)	29 (4.8)	65 (8.8)	**0.005**
Dyslipidemia	678 (50.5)	280 (46.4)	398 (53.8)	**0.007**
Stroke	49 (3.6)	17 (2.8)	32 (4.3)	0.143
Cardiovascular disease	142 (10.6)	28 (4.6)	114 (15.4)	< **0.001**
Atrial fibrillation	51 (3.8)	21 (3.5)	30 (4.1)	0.586
Smoking history	519 (38.6)	210 (34.8)	309 (41.8)	**0.009**
BMI	26.4 (4.4)	25.9 (4.8)	26.8 (3.9)	< **0.001**
eGFR	69.2 (15.5)	67.9 (15.2)	70.3 (15.6)	**0.005**
APOE4 carrier	645 (48.0)	285 (47.3)	360 (48.6)	0.613
Serum uric acid	5.4 (1.3)	4.8 (1.2)	5.8 (1.2)	< **0.001**
MMSE	27.2 (2.6)	27.2 (2.6)	27.1 (2.6)	0.330
Baseline cognitive scores				
Memory	0.19 (0.89)	0.33 (0.96)	0.07 (0.81)	< **0.001**

Executive function	0.14 (1.04)	0.18 (1.03)	0.11 (1.05)	0.179
Language	0.18 (0.95)	0.24 (0.96)	0.14 (0.93)	0.060
Visuospatial function	-0.07 (0.80)	-0.04 (0.78)	-0.10 (0.82)	0.135
Baseline FDG-PET				
Left angular	1.23 (0.18)	1.25 (0.18)	1.21 (0.18)	**< 0.001**
Right angular	1.23 (0.17)	1.25 (0.17)	1.22 (0.18)	**0.018**
Left temporal	1.17 (0.17)	1.19 (0.17)	1.17 (0.17)	**0.044**
Right temporal	1.18 (0.15)	1.19 (0.14)	1.17 (0.15)	0.208
Bilateral posterior cingulum	1.31 (0.19)	1.31 (0.20)	1.31 (0.18)	0.498
HCI	13.44 (7.32)	12.64 (7.03)	14.04 (7.48)	**0.003**

Abbreviations: *APOE4*, apolipoprotein E4; BMI, body mass index; eGFR, estimated glomerular filtration rate; FDG-PET, ^{18}F-Fluorodeoxyglucose positron emission tomography; HCI, hypometabolic convergence index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
Results from the t-test or chi-square test as appropriate. Data are expressed as the mean (standard deviation) or number (%).
Significant *P* values (<0.05) are indicated in bold.

Table 2. Effects of baseline serum uric acid on longitudinal cognitive scores in female and male subjects according to cognitive status

		Total		Normal cognition		MCI		Dementia	
		β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Female	MMSE	0.05 (0.03)	0.079	-0.04 (0.02)	**0.047**	0.10 (0.04)	**0.017**	0.38 (0.20)	0.061
	Memory	0.01 (0.01)	0.235	-0.01 (0.01)	0.369	0.02 (0.01)	**0.020**	0.03 (0.03)	0.256
	Executive	0.01 (0.01)	0.145	-0.01 (0.01)	0.072	0.04 (0.01)	< **0.001**	-0.02 (0.04)	0.513
	Language	0.01 (0.01)	0.144	-0.01 (0.01)	0.289	0.03 (0.01)	**0.010**	0.02 (0.04)	0.614
	Visuospatial	0.003 (0.006)	0.661	-0.01 (0.01)	0.114	0.01 (0.01)	0.182	0.08 (0.06)	0.158
Male	MMSE	-0.001 (0.024)	0.961	-0.04 (0.02)	**0.020**	-0.02 (0.03)	0.592	0.31 (0.18)	0.086
	Memory	0.002 (0.005)	0.669	-0.002 (0.006)	0.769	0.004 (0.006)	0.485	0.01 (0.02)	0.621
	Executive	0.002 (0.006)	0.813	-0.003 (0.008)	0.704	-0.001 (0.009)	0.866	0.03 (0.03)	0.435
	Language	0.004 (0.006)	0.505	-0.01 (0.01)	0.194	0.01 (0.01)	0.158	0.03 (0.03)	0.352
	Visuospatial	-0.01 (0.01)	0.351	-0.01 (0.01)	0.101	-0.005 (0.008)	0.550	0.07 (0.05)	0.153

Abbreviations: *APOE4*, apolipoprotein E4; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination, SE, standard error.
Data are the results of linear mixed models for longitudinal cognitive scores using baseline serum uric acid*year as a predictor. Covariates included age, education, *APOE4*, body mass index, vascular risk factors, eGFR, year, and baseline serum uric acid.
Significant *P* values (<0.05) are indicated in bold.

Table 3. Effects of serum uric acid on longitudinal brain metabolism in female and male subjects according to cognitive status

		Total		Normal cognition		MCI		Dementia	
		β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Female	Left angular	0.001 (0.002)	0.770	-0.003 (0.002)	0.242	0.004 (0.002)	0.102	-0.004 (0.008)	0.660
	Right angular	0.0001 (0.0017)	0.933	-0.003 (0.002)	0.114	0.003 (0.002)	0.127	-0.002 (0.008)	0.809
	Left temporal	0.002 (0.002)	0.294	-0.002 (0.002)	0.237	0.005 (0.002)	**0.012**	0.0004 (0.0076)	0.963
	Right temporal	0.0003 (0.0015)	0.834	-0.003 (0.002)	0.127	0.003 (0.002)	0.177	0.004 (0.008)	0.670
	Bilateral cingulum	0.002 (0.002)	0.151	0.001 (0.003)	0.583	0.004 (0.002)	0.086	0.001 (0.007)	0.869
	HCI	-0.08 (0.06)	0.185	0.06 (0.06)	0.359	-0.20 (0.08)	**0.010**	-0.34 (0.34)	0.321
Male	Left angular	-0.001 (0.002)	0.581	0.001 (0.002)	0.710	-0.001 (0.002)	0.491	-0.001 (0.007)	0.894
	Right angular	-0.002 (0.002)	0.220	-0.002 (0.002)	0.368	-0.002 (0.002)	0.271	-0.002 (0.006)	0.787
	Left temporal	-0.001 (0.001)	0.324	-0.0001 (0.0021)	0.944	-0.002 (0.002)	0.315	-0.008 (0.007)	0.213
	Right temporal	-0.002 (0.001)	0.127	-0.002 (0.002)	0.449	-0.002 (0.002)	0.221	-0.008 (0.006)	0.239
	Bilateral cingulum	-0.0003 (0.0015)	0.839	-0.0001 (0.0025)	0.963	-0.001 (0.002)	0.554	0.0003 (0.0058)	0.961
	HCI	0.06 (0.06)	0.301	0.01 (0.07)	0.840	0.10 (0.07)	0.147	0.25 (0.27)	0.347

Abbreviations: *APOE4*, apolipoprotein E4; eGFR, estimated glomerular filtration rate; HCI, hypometabolic convergence index; MCI, mild cognitive impairment, SE, standard error.

Data are the results of linear mixed models for longitudinal brain metabolism using baseline serum uric acid*year as a predictor. Covariates included age, education, *APOE4*, body mass index, vascular risk factors, eGFR, year, and baseline serum uric acid.
Significant *P* values (<0.05) are indicated in bold.

Table 4. Effects of baseline serum uric acid, *APOE4*, and their interaction on longitudinal cognitive scores and brain metabolism in female MCI patients

		Uric acid*year		*APOE4**year		Uric acid**APOE4**year	
		β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Cognition	MMSE	-0.02 (0.05)	0.633	-2.26 (0.43)	< **0.001**	0.34 (0.09)	< **0.001**
	Memory	0.01 (0.01)	0.139	-0.11 (0.08)	0.179	0.01 (0.02)	0.562
	Executive	0.02 (0.01)	0.058	-0.25 (0.11)	**0.020**	0.04 (0.02)	0.083
	Language	0.01 (0.01)	0.519	-0.33 (0.10)	**0.001**	0.05 (0.02)	**0.020**
	Visuospatial	-0.004 (0.010)	0.726	-0.31 (0.09)	**0.001**	0.05 (0.02)	**0.009**
Brain metabolism	Left angular	0.0001 (0.0028)	0.968	-0.06 (0.03)	**0.017**	0.01 (0.01)	0.072
	Right angular	-0.0001 (0.0027)	0.984	-0.06 (0.02)	**0.020**	0.01 (0.01)	0.088
	Left temporal	0.002 (0.002)	0.522	-0.05 (0.02)	**0.014**	0.01 (0.005)	0.082
	Right temporal	-0.0001 (0.0024)	0.959	-0.04 (0.02)	**0.038**	0.01 (0.005)	0.155
	Bilateral cingulum	0.001 (0.003)	0.723	-0.05 (0.02)	0.052	0.01 (0.005)	0.174
	HCI	-0.07 (0.09)	0.483	2.84 (0.83)	**0.001**	-0.42 (0.18)	**0.017**

Abbreviations: *APOE4*, apolipoprotein E4; eGFR, estimated glomerular filtration rate; HCI, hypometabolic convergence index; MCI, mild cognitive impairment; SE, standard error.

Data are the results of linear mixed models for longitudinal cognitive scores or brain metabolism using baseline serum uric acid*year, *APOE4**year, and baseline serum uric acid**APOE4**year as predictors. Covariates included age, education, *APOE4*, body mass index, eGFR, vascular risk factors, year, baseline serum uric acid, and baseline serum uric acid**APOE4*.
Significant *P* values (<0.05) are indicated in bold.

Table 5. Effects of baseline serum uric acid on longitudinal cognitive scores with and without consideration for HCI in the female MCI subgroup

		Female MCI				Female MCI with *APOE4*			
		Model 1		Updated model		Model 3		Updated model	
	Predictors	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
MMSE	Uric acid*year	0.10 (0.04)	**0.017**	0.01 (0.04)	0.804	0.33 (0.09)	< **0.001**	0.09 (0.09)	0.347
	HCI			-0.29 (0.02)	< **0.001**			-0.28 (0.03)	< **0.001**
Memory	Uric acid*year	0.02 (0.01)	**0.020**	0.01 (0.01)	0.332	0.02 (0.01)	0.095	0.02 (0.02)	0.290
	HCI			-0.06 (0.01)	< **0.001**			-0.06 (0.01)	< **0.001**
Executive	Uric acid*year	0.04 (0.01)	< **0.001**	0.01 (0.01)	0.413	0.06 (0.02)	**0.002**	0.03 (0.03)	0.259
	HCI			-0.07 (0.01)	< **0.001**			-0.07 (0.01)	< **0.001**
Language	Uric acid*year	0.03 (0.01)	**0.010**	0.01 (0.01)	0.610	0.06 (0.02)	**0.002**	0.01 (0.02)	0.672
	HCI			-0.06 (0.01)	< **0.001**			-0.07 (0.01)	< **0.001**
Visuospatial	Uric acid*year	0.01 (0.01)	0.182	0.01 (0.01)	0.492	0.05 (0.02)	**0.008**	0.01 (0.02)	0.808
	HCI			-0.04 (0.01)	< **0.001**			-0.04 (0.01)	< **0.001**

Abbreviations: *APOE4*, apolipoprotein E4; eGFR, estimated glomerular filtration rate; HCI, hypometabolic convergence index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SE, standard error.
Data are the results of linear mixed models for longitudinal cognitive scores performed in female MCI patients using baseline serum uric acid*year as a predictor. Covariates included age, education, body mass index, vascular risk factors, eGFR, *APOE4*, year, and baseline serum

uric acid (Model 1) and without *APOE4* (Model 3). To evaluate the effect of baseline serum uric acid level on longitudinal cognitive decline being independent of brain metabolism. HCI was further included from the Model 1 and 3 (Updated model).
Significant *P* values (<0.05) are indicated in bold.