ORIGINAL ARTICLE

Does serum uric acid act as a modulator of cerebrospinal fluid Alzheimer's disease biomarker related cognitive decline?

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Background and purpose: The association of serum uric acid, cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) and longitudinal cognitive decline was evaluated using the AD Neuroimaging Initiative database.

Methods: In 271 healthy subjects, 596 mild cognitive impairment patients and 197 AD patients, serum uric acid and CSF AD biomarkers were measured at baseline, and Mini-Mental State Examination and AD Assessment Scale – Cognitive Subscale (ADAS-cog) were assessed serially (mean duration, 2.9 years). The effect of uric acid on longitudinal cognitive decline was evaluated using linear mixed effect models for Mini-Mental State Examination and ADAS-cog scores in female and male subjects separately, with possible confounders controlled (model 1). To determine the effects of uric acid independent of CSF biomarker ($A\beta_{1–42}$ or tau) and to test whether the detrimental effects of CSF biomarker differ according to uric acid, CSF biomarker and its interaction with uric acid were further included in model 1 (model 2).

Results: Higher levels of uric acid were associated with slower cognitive decline, particularly in the mild cognitive impairment and dementia subgroups, and more prominently in female subjects. Model 2 with CSF $A\beta_{1–42}$ showed that higher levels of uric acid were associated with a slower cognitive decline and alleviated the detrimental effect of $A\beta_{1–42}$ on cognitive decline. Model 2 with CSF tau showed that higher levels of uric acid alleviated the detrimental effect of tau on cognitive decline in female subjects but not in male subjects.

Conclusion: Higher levels of uric acid had protective effects on longitudinal cognitive decline independent of and interactively with CSF AD biomarkers.

Introduction

The influence of serum uric acid on degenerative dementia is controversial. The antioxidant effect of serum uric acid [1] is regarded as a mechanism explaining the association between lower serum uric acid and increased risk of Parkinson's disease [2] or dementia [3,4]. However, uric acid is also associated with increased risks of cardiovascular [5,6] and cerebrovascular diseases [7] that could increase the risk of cognitive impairment. Previous studies showed conflicting results regarding the association between serum uric acid and cognitive function [4,8]. A previous study, however, showed that higher levels of uric acid are associated with a decreased risk of dementia and better cognitive function later in life after controlling for cardiovascular risk factors [4], which raises a possibility of serum uric acid as a protective factor for cognitive decline and dementia.

Alzheimer's disease (AD) is the most common cause of degenerative dementia, and AD pathology closely correlates with cognitive impairment in healthy subjects [9], those with mild cognitive impairment (MCI) [10] and demented patients [11,12]. Additionally, cerebrospinal fluid (CSF) AD biomarkers, which reflect AD pathology [13], predict cognitive decline in

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non-demented subjects [14] and patients with early dementia [15]. Considering the potential protective effect of serum uric acid in cognitive decline, it was hypothesized that serum uric acid would have a modifying effect on the relationship between CSF AD biomarkers and cognitive decline. In this study, this hypothesis was tested using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

Methods

Participants and cognitive measures

Data used in the current study were obtained from the ADNI database (http://adni.loni.usc.edu/data-samples/access-data). The ADNI is a large, multicenter, longitudinal neuroimaging study, which was launched in 2003 by the US National Institute of Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations. The ADNI has three phases: the first ADNI (ADNI 1), the ADNI Grand Opportunities (ADNI-GO) and the second ADNI (ADNI 2) [16]. ADNI 1 enrolled and followed up over 800 subjects in the original three cohorts: healthy controls, amnestic MCI patients and mild AD subjects. ADNI-GO enrolled additional MCI subjects with a milder degree of memory impairment (early MCI). ADNI 2 supported the ongoing follow-up of the ADNI 1 and ADNI-GO cohorts and recruited additional healthy control, MCI and AD subjects.

Demographic data and information on cardiovascular risk factors including the presence of diabetes mellitus, hypertension, hypercholesterolemia, heart disease, stroke and smoking history were also available from the ADNI website. In this study, data that were previously collected across 50 sites were used. Study subjects provided written informed consent for data collection at the time of enrolment and completed questionnaires approved by each participating site's Institutional Review Board (IRB). The complete list of IRBs from the ADNI sites can be accessed at http://adni.loni.ucla.edu/about/data-statistics/.

Diagnosis of MCI required a patient-reported memory complaint, objective memory deficits, intact functional activities, a Clinical Dementia Rating Scale [17] global score of 0.5 and a Mini-Mental State Examination (MMSE) [18] score of 24 or higher. AD patients met the criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association for probable AD [19]. The total scores for the MMSE and AD Assessment Scale – Cognitive Subscale (ADAS-cog) [20] were used as cognitive measures.

Cerebrospinal fluid biomarker data

Cerebrospinal fluid biomarker data were downloaded on 5 January 2015 from the ADNI website, where the ADNI grant and all ADNI data are posted for public access. The detailed procedures for acquiring and processing CSF for biomarker analysis were described previously [21]. Baseline CSF data records were identified for 271 healthy control subjects, 296 MCI cases and 197 AD patients. The mean interval from uric acid measurement and CSF sampling time was 0.2 years (SD 0.4) and was not different according to the baseline diagnosis. In a single subject, CSF $A\beta_{1–42}$, tau, total tau (t-tau) and phospho-tau (p-tau) were measured by multiple laboratories [21]. Specifically, there were 394 data for $A\beta_{1–42}$ and 280 data for tau in healthy subjects; 939 data for $A\beta_{1–42}$ and 749 data for tau in MCI patients; and 305 data for $A\beta_{1–42}$ and 204 data for tau in dementia patients. Therefore, values from multiple laboratories were averaged to acquire one baseline CSF $A\beta_{1–42}$ and tau value respectively.

Uric acid data

Amongst 1122 participants with CSF data, serum uric acid data were available for 281 healthy subjects, 624 MCI patients and 206 AD patients. The exact procedures of collection and processing of clinical chemistry data can be found in the *ADNI Procedures Manual* (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). These cases were identified in the Biospecimen data section of the ADNI website. The serum uric acid level was treated as a continuous variable [mean (SD), 5.4 (1.4)]. The serum uric acid level was also treated as a categorical variable and subjects were divided into three groups according to the tertiles of the serum uric acid level variable. As male subjects exhibited a significantly higher level of serum uric acid than female subjects, female and male subjects were divided using gender-specific cut-off values (female 4.2 and 5.4; male 5.3 and 6.4).

Statistical analysis

All statistical analyses were performed using the SPSS statistical package. Baseline demographic and clinical data were evaluated using an analysis of variance, an independent *t* test or a chi-squared test as appropriate. Because CSF biomarkers were tested multiple times in

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the different laboratories, baseline CSF biomarker results across multiple laboratories were averaged (Table 1).

Evaluations were performed 4.70 (2.07) times for ADAS-cog and 4.69 (2.04) times for MMSE. The follow-up durations were 2.87 (1.95) years for ADAS-cog and 2.88 (1.95) years for MMSE. To test the association between serum uric acid and cognitive decline, linear mixed effect models were performed using the MMSE score and ADAS-cog score at each evaluation time as response variables and the interaction between serum uric acid level and the time interval from uric acid evaluation to each cognitive evaluation (time) as a fixed effect. Age, sex, education, body mass index (BMI), race, *apolipoprotein E4* (*APOE4*) carrier, diagnosis at the baseline CSF sampling time and cardiovascular risk factors were also included as covariates, and the sites where subjects were enrolled were included as a random effect (model 1). As there was a significant gender difference in serum uric acid level and a significant three-way interaction effect of serum uric acid, gender and time (described in the Results section), all tests were performed using linear mixed effect models in female and male subjects separately. To see the difference in the pattern of the uric acid effect on cognitive decline according to the baseline diagnosis, the model 1 analyses were also performed in the baseline healthy subjects, MCI and dementia subgroups respectively. In these analyses, the baseline diagnosis was not included as a covariate. Serum uric acid was also treated as a categorical variable (gender-specific tertile groups as described above) using the middle tertile group as a reference group in order to identify any non-linear effect of serum uric acid.

To test the independent effect of serum uric acid on cognitive decline, controlling for the effect of the CSF AD biomarker (CSF $A\beta_{1–42}$ or CSF tau), and to determine whether serum uric acid has a modifying

Table 1 Baseline demographic and clinical data

	Total	Female	Male	*P*
Number	1064	466	598	
Age, years	73.7 (7.4)	72.7 (7.4)	74.5 (7.3)	<0.001
Education, years	16.0 (2.8)	15.3 (2.6)	16.5 (2.8)	<0.001
Serum uric acid	5.4 (1.4)	4.9 (1.3)	5.9 (1.3)	<0.001
APOE4 carrier[a], *N* (%)	494 (47.2)	213 (46.6)	281 (47.7)	0.724
Cardiovascular risk factors				
Diabetes mellitus, *N* (%)	95 (8.9)	26 (5.6)	69 (11.5)	0.001
Hypertension, *N* (%)	797 (74.9)	338 (72.5)	459 (76.8)	0.115
Hyperlipidemia, *N* (%)	547 (51.4)	217 (46.6)	330 (55.2)	0.005
Heart disease, *N* (%)	119 (11.2)	22 (4.7)	97 (16.2)	<0.001
Stroke, *N* (%)	52 (4.9)	20 (4.3)	32 (5.4)	0.427
Smoking history, *N* (%)	267 (25.1)	92 (19.7)	175 (29.3)	<0.001
Baseline diagnosis	1064	466	598	0.030
Healthy, *N* (%)	271 (25.5)	137 (29.4)	134 (22.4)	
Mild cognitive impairment, *N* (%)	596 (56.0)	244 (52.4)	352 (58.9)	
Dementia, *N* (%)	197 (18.5)	85 (18.2)	112 (18.7)	
Body mass index	26.9 (4.7)	26.7 (5.4)	27.0 (4.1)	0.305
Baseline CSF biomarkers				
$A\beta_{1–42}$	174.4 (65.2)	177.5 (65.3)	172.1 (65.1)	0.178
p-tau	35.8 (21.2)	36.6 (23.3)	35.3 (19.5)	0.332
Tau	93.1 (55.1)	99.9 (61.6)	87.8 (48.9)	0.001
Tau/$A\beta_{1–42}$	0.63 (0.52)	0.67 (0.57)	0.60 (0.48)	0.048
Baseline ADAS-cog	10.8 (6.6)	10.1 (6.7)	11.3 (6.4)	0.003
Baseline MMSE	27.2 (2.6)	27.4 (2.6)	27.1 (2.6)	0.044
Follow-up frequency				
ADAS-cog	4.70 (2.07)	4.68 (2.02)	4.72 (2.11)	0.717
MMSE	4.69 (2.04)	4.63 (1.95)	4.73 (2.11)	0.447
Follow-up duration				
ADAS-cog	2.87 (1.95)	2.85 (1.93)	2.89 (1.96)	0.769
MMSE	2.88 (1.95)	2.87 (1.93)	2.90 (1.97)	0.809

ADAS-cog, Assessment Scale – Cognitive Subscale; *APOE4*, *apolipoprotein E4*; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau. Data are expressed as mean (standard deviation) or number (%). *P* values are the results of independent *t*-tests and chi-squared tests as appropriate.

[a]*APOE* data were unavailable for 18 subjects.

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effect on the relationship between the CSF AD biomarker and cognitive decline, the interaction between serum uric acid and time, the interaction between the baseline CSF AD biomarker and time, the interaction between serum uric acid and the baseline CSF AD biomarker, and three-way interactions (serum uric acid × baseline CSF AD biomarkers × time) were simultaneously included as fixed effects (model 2; Table 3). Longitudinal effects of baseline CSF AD biomarkers on cognitive decline were also tested in the lower, middle and higher uric acid tertile groups separately.

Results

Baseline demographics and clinical comparison

A comparison of baseline demographics and clinical data is presented in Table 1. The mean age of the study subjects was 73.7 years; 43.8% were female, and the mean duration of education was 16.0 years. Male subjects more frequently had cardiovascular risk factors, including diabetes mellitus, hyperlipidemia, heart disease and smoking history, than female subjects. When subjects were categorized according to the gender-specific uric acid tertile groups, mean BMI and the distributions of baseline diagnoses and hypertension were different amongst the three tertile groups (Table S1). *Post hoc* analysis with Bonferroni's correction showed that the middle tertile group had a lower BMI than the higher tertile group but had a higher BMI than the lower tertile group. Hypertension was more common in the higher tertile group than in the middle and lower tertile groups. Other factors including baseline age, proportions of subjects with *APOE4* carrier, history of diabetes mellitus, hyperlipidemia, heart disease, stroke and smoking history, and baseline MMSE and ADAS-cog scores did not differ across the three uric acid tertile groups.

Comparison of the rate of cognitive decline according to serum uric acid level

There were significant three-way interaction effects of serum uric acid (as a continuous variable), gender and time on longitudinal cognitive decline [for MMSE, beta (95% confidence interval) = −0.11 (−0.20, −0.02), $P = 0.013$; for ADAS-cog, beta (95% confidence interval) = 0.22 (0.03, 0.42), $P = 0.023$]. Therefore, as stated in the statistical analysis section, all linear mixed effect models were performed in female and male subjects separately.

Overall, amongst female subjects, linear mixed models (model 1) showed that a higher serum uric acid level was associated with a slower rate of cognitive decline in MMSE (decreased score) and ADAS-cog (increased score) (Table 2). When the effects of serum uric acid were tested separately according to baseline

Table 2 Effects of serum uric acid on longitudinal cognitive changes

Gender	Baseline diagnosis	MMSE		ADAS-cog	
		Beta (95% CI)	*P*	Beta (95% CI)	*P*
Female	All subjects	0.18 (0.11, 0.24)	<0.001	−0.32 (−0.47, −0.17)	<0.001
	Healthy subjects	−0.03 (−0.06, 0.005)	0.093	0.10 (0.02, 0.19)	0.019
	MCI	0.20 (0.09, 0.31)	<0.001	−0.50 (−0.74, −0.26)	<0.001
	Dementia	0.47 (0.11, 0.83)	0.012	−0.54 (−1.27, 0.18)	0.143
Male	All subjects	0.06 (0.005, 0.12)	0.034	−0.11 (−0.23, 0.02)	0.094
	Healthy subjects	−0.01 (−0.06, 0.04)	0.633	0.01 (−0.11, 0.12)	0.883
	MCI	0.01 (−0.07, 0.09)	0.813	−0.001 (−0.16, 0.16)	0.993
	Dementia	0.37 (0.04, 0.71)	0.029	−0.36 (−1.01, 0.29)	0.280

ADAS-cog, Assessment Scale – Cognitive Subscale; *APOE4*, *apolipoprotein E4*; CI, confidence interval; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Data are the results of linear mixed effect models for MMSE or ADAS-cog scores that were calculated for all subjects and separately for each subgroup according to gender and diagnosis of healthy, MCI or dementia at the first CSF study. The laboratories where biomarker analyses were performed and the sites where subjects were enrolled were treated as random effects. To evaluate the effects of serum uric acid on longitudinal changes in cognition, the interaction between serum uric acid level and the interval from uric acid evaluation to cognitive evaluation (time) was used as a predictor. Baseline age, education, race, *APOE4* carrier, body mass index, interval from uric acid evaluation to each cognitive evaluation time, and cardiovascular risk factors were used as covariates. For analyses on all subjects, baseline diagnosis was additionally included as a covariate. Beta (95% CI) and *P* were calculated for the interaction effect between time and serum uric acid level.

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diagnosis, the direction of the beta coefficient in healthy subjects was opposite to those in the MCI and dementia subgroups. A higher serum uric acid level was associated with a slower cognitive decline in MMSE and ADAS-cog scores in subjects with baseline MCI diagnosis and in MMSE scores in subjects with baseline dementia diagnosis, whilst it was conversely associated with a faster cognitive decline in ADAS-cog scores in baseline healthy subjects.

When the uric acid tertile group was used as a predictor instead of serum uric acid level, the lower uric acid tertile group exhibited faster cognitive decline in MMSE and ADAS-cog scores than the middle tertile group, whilst the higher tertile group showed slower rates of cognitive decline in female subjects overall (Table S2). In the subgroup analysis according to baseline diagnosis, the results were similar to those from analyses using serum uric acid level as a predictor. Although statistical significance was not reached, in healthy subjects the lower tertile group showed a slower rate of cognitive decline and the higher tertile group showed a faster rate of cognitive decline than the middle tertile group. In subjects with baseline MCI and those with dementia, however, the lower tertile group showed a faster rate of cognitive decline and the higher tertile group showed a slower rate of cognitive decline than the middle tertile group, although statistical significance was reached only in the MCI subgroup (the higher tertile group had a slower MMSE decline and the lower tertile group exhibited faster ADAS-cog deterioration than the middle tertile group).

Amongst all male subjects, a higher serum uric acid level was associated with a slower MMSE decline and tended to be associated with a slower ADAS-cog deterioration. When the effects of serum uric acid were tested separately according to baseline diagnosis, the direction of the beta coefficient in healthy subjects was opposite to those in the MCI and dementia subgroups. In subjects with baseline dementia diagnosis, a higher serum uric acid level was associated with a slower cognitive decline in MMSE scores, although there was no significant association between serum uric acid levels and the rate of cognitive change in subjects with baseline MCI and healthy subjects.

When the uric acid tertile group was used as a predictor instead of serum uric acid level, the higher tertile group tended to show slower rates of cognitive decline than the middle tertile group in ADAS-cog score, whilst the higher and lower tertile groups had comparable rates of cognitive decline in MMSE and ADAS-cog scores to the reference group in male subjects overall (Table S2). Subgroup analyses according to baseline diagnosis showed that, in healthy subjects, the lower tertile group had a slower rate of cognitive decline (significant for MMSE), whilst the higher tertile group had a faster rate of cognitive decline (significant for ADAS-cog). In subjects with baseline MCI and dementia diagnosis, the middle tertile group showed comparable rates of cognitive decline with those of the lower and higher tertile groups.

Effects of serum uric acid level and its interaction with CSF AD biomarkers on longitudinal cognitive decline

In female subjects, when the effect of CSF $A\beta_{1–42}$ and its interaction effect with serum uric acid level were simultaneously considered, a higher serum uric acid level was associated with a slower cognitive decline in MMSE and ADAS-cog scores, and the detrimental effect of CSF $A\beta_{1–42}$ was less prominent amongst those with a higher serum uric acid level (Table 3). When the effect of CSF tau and its interaction effect with serum uric acid level were considered, serum uric acid was not associated with the rate of cognitive decline; however, the detrimental effect of CSF tau was less prominent amongst those with a higher serum uric acid level (Table 3). When the uric acid tertile group was used as a predictor instead of serum uric acid level (Table S3), the higher tertile group exhibited slower cognitive decline than the middle tertile group, and the detrimental effect of CSF $A\beta_{1–42}$ was less prominent in the higher tertile group than in the middle tertile group. The rate of cognitive decline and the degree of the detrimental effect of CSF $A\beta_{1–42}$ were comparable between the lower and the middle tertile groups. When the effect of CSF tau and its interaction effect with the uric acid tertile group were simultaneously considered, the higher and lower tertile groups had comparable rates of cognitive decline relative to the middle tertile group; however, the detrimental effect of CSF tau was more prominent in the lower tertile group and less prominent in the higher tertile group relative to that in the middle tertile group.

In male subjects, when the effect of CSF $A\beta_{1–42}$ and its interaction effect with serum uric acid level were simultaneously considered, a higher serum uric acid level was associated with a slower cognitive decline in MMSE and ADAS-cog scores, and the detrimental effect of CSF $A\beta_{1–42}$ on ADAS-cog score was less prominent amongst those with a higher serum uric acid level (Table 3). When the effect of CSF tau and its interaction effect with serum uric acid level were considered, the effect of serum uric acid and its interaction effect with CSF tau on cognitive decline were not significant (Table 3). When uric acid tertile group was used as a predictor instead of serum uric acid

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Table 3 Effects of serum uric acid, baseline CSF AD biomarkers and their interaction on longitudinal cognitive changes

		MMSE		ADAS-cog	
Gender	Model and predictors	Beta (95% CI)	*P*	Beta (95% CI)	*P*
Female	$A\beta_{1-42}$ model				
	Uric acid	0.315 (0.194, 0.437)	<0.001	−0.646 (−0.956, −0.337)	<0.001
	$A\beta_{1-42}$	0.009 (0.006, 0.012)	<0.001	−0.020 (−0.029, −0.011)	<0.001
	Uric acid × $A\beta_{1-42}$	−0.001 (−0.002, −0.0003)	0.003	0.002 (0.001, 0.004)	0.011
	Tau model				
	Uric acid	−0.109 (−0.242, 0.025)	0.110	0.160 (−0.119, 0.438)	0.260
	Tau	−0.025 (−0.032, −0.018)	<0.001	0.048 (0.034, 0.062)	<0.001
	Uric acid × tau	0.003 (0.002, 0.004)	<0.001	−0.005 (−0.008, −0.002)	<0.001
Male					
	$A\beta_{1-42}$ model				
	Uric acid	0.163 (0.042, 0.284)	0.008	−0.452 (−0.718, −0.187)	0.001
	$A\beta_{1-42}$	0.006 (0.002, 0.011)	0.008	−0.019 (−0.029, −0.008)	<0.001
	Uric acid × $A\beta_{1-42}$	−0.001 (−0.001, 0.0001)	0.113	0.002 (0.001, 0.004)	0.007
	Tau model				
	Uric acid	−0.006 (−0.139, 0.126)	0.925	0.138 (−0.147, 0.423)	0.341
	Tau	−0.010 (−0.019, −0.002)	0.018	0.029 (0.011, 0.048)	0.002
	Uric acid × tau	0.001 (−0.001, 0.002)	0.411	−0.002 (−0.006, 0.001)	0.113

AD, Alzheimer's disease; ADAS-cog, Assessment Scale – Cognitive Subscale; *APOE4*, *apolipoprotein E4*; CI, confidence interval; CSF, cerebrospinal fluid.

Data are the results of linear mixed effect models for MMSE or ADAS-cog scores calculated for male and female subjects separately. The laboratories where biomarker analyses were performed and the sites where subjects were enrolled were treated as random effects. To evaluate the effects of serum uric acid, CSF AD biomarkers (CSF $A\beta_{1-42}$ or CSF tau), their interaction effects on longitudinal changes in cognition, and the interaction terms [those between CSF AD biomarker (CSF $A\beta_{1-42}$ or CSF tau) and the interval from baseline to each follow-up time for cognitive evaluation (time), those between serum uric acid level and time, and the three-way interaction terms for serum uric acid level, CSF AD biomarker and time] were used as predictors. Baseline age, sex, education, body mass index, race, *APOE4* carrier, time, baseline diagnosis, cardiovascular risk factors, and the interaction term between serum uric acid level and CSF AD biomarker were used as covariates. Beta (95% CI) and *P* were calculated for the interaction effect between serum uric acid level and time, between CSF AD biomarker (CSF $A\beta_{1-42}$ or CSF tau) and time, and between the three-way interactions (serum uric acid level × CSF AD biomarker × time).

level (Table S3), in the CSF $A\beta_{1-42}$ model the higher tertile group exhibited slower cognitive decline than the middle tertile group, and the detrimental effect of CSF $A\beta_{1-42}$ was less prominent in the higher tertile group than in the middle tertile group. When the effect of CSF tau and its interaction effect with the uric acid tertile group were simultaneously considered (tau model), the rate of cognitive decline and the degree of the detrimental effect of CSF $A\beta_{1-42}$ were comparable amongst all three uric acid tertile groups. The actual degree of the detrimental effect of CSF $A\beta_{1-42}$ and CSF tau in the three uric acid tertile groups is presented in Table S4, Fig. 1 (female subjects) and Fig. 2 (male subjects).

Discussion

In the current study, serum uric acid levels modified the relationship between CSF AD biomarker and longitudinal cognitive decline, although the degree of modification was different according to gender. Specifically, a higher serum uric acid level alleviated the detrimental effect of CSF $A\beta_{1-42}$ and CSF tau on the longitudinal deterioration of MMSE and ADAS-cog scores in female subjects, and it also alleviated the detrimental effect of CSF $A\beta_{1-42}$ on ADAS-cog scores; however, it did not have a significant impact on the detrimental effect of CSF tau. Moreover, it was found that a higher serum uric acid level was associated with a slower rate of longitudinal cognitive deterioration, independent of the detrimental effects of baseline CSF $A\beta_{1-42}$. Taken together, these findings suggest that a higher serum uric acid level has a protective effect on cognitive decline independent of and interactively with CSF AD biomarker and that this protective effect is more prominent in female subjects.

Our major finding is that serum uric acid level and CSF $A\beta_{1-42}$ had significant interaction effects on cognitive decline. A higher serum uric acid level alleviated the detrimental effects of CSF $A\beta_{1-42}$ on cognitive decline. To the best of our knowledge, this is the first study investigating interaction effects of CSF AD biomarkers and serum uric acid on cognitive decline. According to previous studies, uric acid inhibits amyloid-beta-induced neuronal apoptosis [22] and

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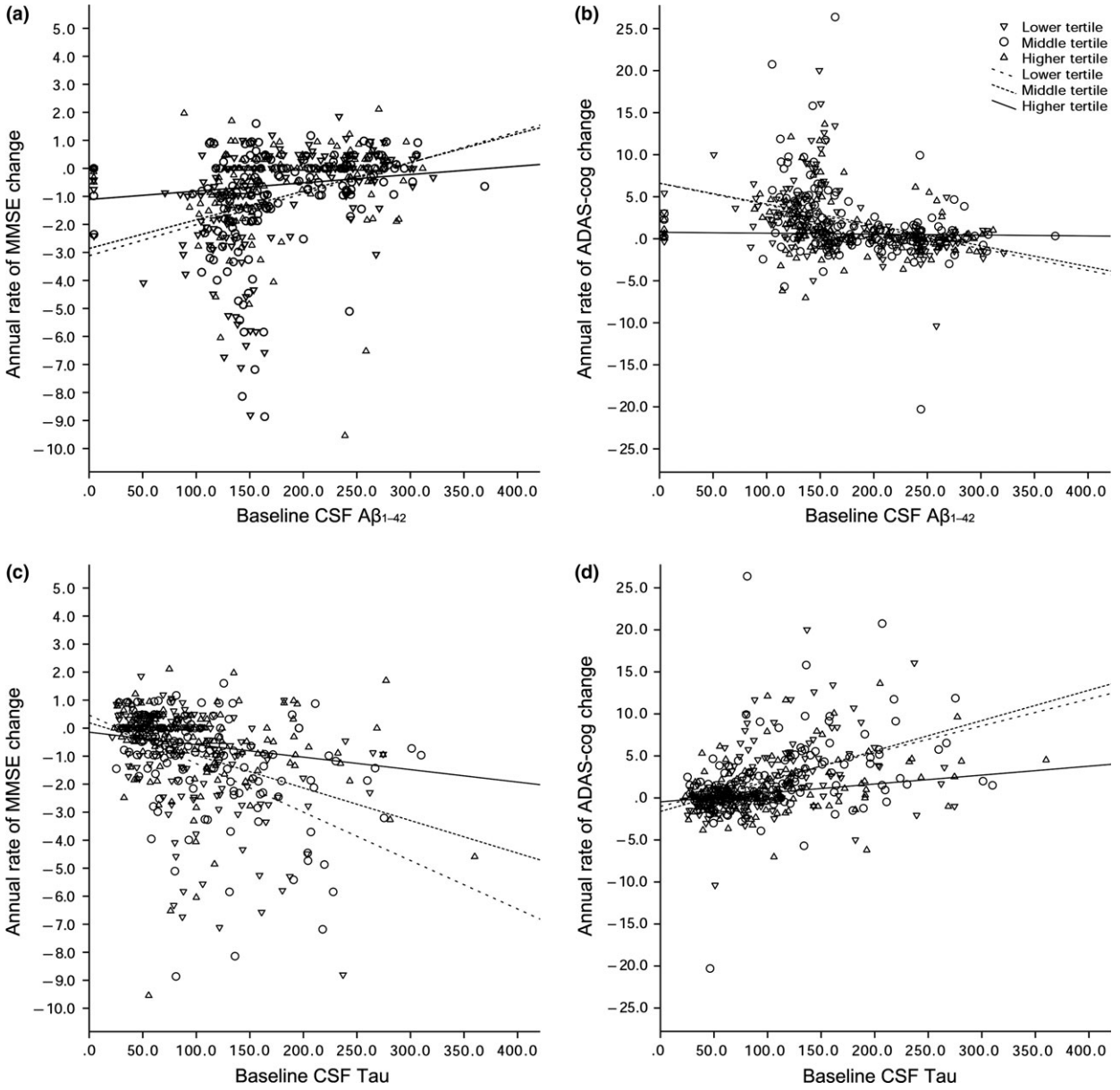

Figure 1 Relationship of baseline CSF biomarkers and annualized changes in cognitive scores (MMSE and ADAS-cog scores) according to gender-specific uric acid tertile groups in female subjects. Scatter plots and lines of linear best fit for each tertile group are presented. ADAS-cog, Assessment Scale – Cognitive Subscale; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination.

cholinergic dysfunction [23] through the inhibition of oxidative stress from peroxynitrite. Uric acid is a natural antioxidant that reduces oxidative stress by scavenging free radicals *in vitro* [1,24,25]. Considering that interaction between oxidative stress and amyloid beta amplifies neuronal damage in AD [26,27], the antioxidant effect of uric acid could mitigate the detrimental effects of amyloid beta on cognition.

A higher serum uric acid level was found to have beneficial effects on cognitive decline after adjustment for the detrimental effect of CSF $A\beta_{1-42}$; however, this was not the case after controlling for the detrimental effect of CSF tau and its interaction with serum uric acid. This suggests that the beneficial effect of serum uric acid on cognition is dependent on the detrimental effect of tau itself or the modification of the detrimental effect from tau pathology. Oxidative stress is regarded as an important factor in the initiation and progression of neurodegeneration [28], and previous studies have shown that oxidative stress enhances tau-induced neurodegeneration in *Drosophila* [29] and chronic oxidative stress increases the level of tau

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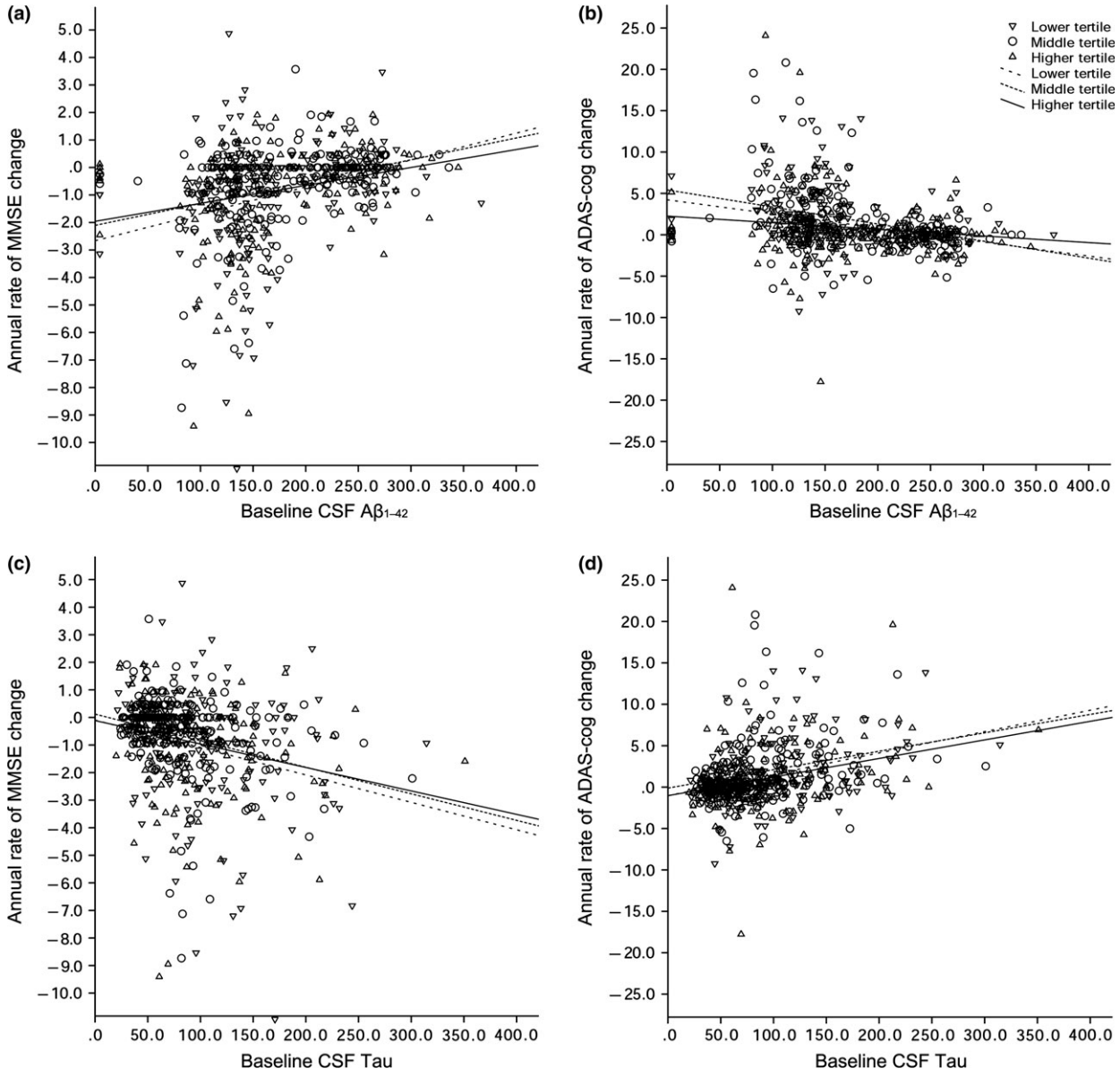

Figure 2 Relationship of baseline CSF biomarkers and annualized changes in cognitive scores (MMSE and ADAS-cog scores) according to gender-specific uric acid tertile groups in male subjects. Scatter plots and lines of linear best fits for each tertile group are presented. ADAS-cog, Assessment Scale – Cognitive Subscale; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination.

pathology [30,31]. Therefore, the beneficial effects of serum uric acid on cognitive decline could be explained by the complex relationship between oxidative stress, tau and neurodegeneration. Considering that oxidative stress markers are increased and more localized to the synapses in the brains of AD patients [32], rescue of the synaptic dysfunction could be a possible mechanism for the beneficial effect of uric acid.

The beneficial effects of serum uric acid were more prominent in female subjects than in male subjects. Additionally, the interaction effect of serum uric acid and CSF tau was significant in female subjects but not in male subjects. These results might be associated with the more prevalent vascular risk factors in male subjects, including diabetes mellitus, hyperlipidemia, smoking history and heart disease, which can result in more prominent vascular pathology. Prior research indicated that higher levels of uric acid are associated with both greater cerebral ischaemia [33] and reduced cognitive performance on tests that are more frequently affected by vascular pathology [34]. Moreover, it has been demonstrated that the association between uric acid and cognition is mediated by vascular white

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matter changes in older adults [35]. Therefore, our results suggest that the risk of AD may be reduced with greater uric acid levels; however, the risk of vascular cognitive decline may increase as uric acid level increases. This point of view is further supported by our results (Table 2) indicating that the beta coefficients for the effect of serum uric acid in the subgroup with healthy subjects were in the opposite direction from those in the subgroups with MCI and dementia and that the dementia subgroup had a higher amplitude of beta coefficients than the MCI subgroup, which might have had a more prevalent AD pathology.

Our study has some limitations. First, the ADNI dataset is not designed to investigate the effect of serum uric acid level, and therefore there could be methodological inconsistencies in serum uric acid assessments, even though sites where subjects were enrolled were controlled for. Secondly, subjects recruited into ADNI might not be representative of the general population and therefore our results should be interpreted cautiously. Thirdly, the confounding effect of cerebral ischaemia and vascular pathology was not considered.

Despite these limitations, our results suggest that serum uric acid level had a protective effect on longitudinal cognitive decline independently and interactively with CSF biomarkers.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of baseline demographic and clinical data according to gender-specific uric acid tertile groups.
Table S2. Comparison of the rate of cognitive changes among gender-specific uric acid tertile groups in all subjects, healthy subjects, MCI, and dementia patients.
Table S3. Effects of gender-specific uric acid tertile group, baseline CSF AD biomarkers and their interaction on longitudinal cognitive changes.
Table S4. Subgroup analysis for the associations of baseline CSF AD biomarkers with longitudinal changes in cognition in the three uric acid tertile groups.

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