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Original Article

Serum Uric Acid Levels Associated with Outcomes of Neurodegenerative Disorders and Brain Health: Findings from the UK Biobank

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ABSTRACT

Background: The relationship between serum uric acid (SUA) levels and brain-related health remains uncertain.
Objectives: This study aimed to investigate the relationship between SUA levels and some neurodegenerative disorders and brain structure.
Design: A longitudinal study.
Setting and participants: 384,517 participants who did not have stroke, dementia, and Parkinsonism, with complete urate testes and covariates were included.
Measurements: Cox proportional hazards models, competing risk models, and restricted cubic spine models were applied.
Results: During the median follow-up time of 12.7 years (interquartile range [IQR]:12.0, 13.5), 7821 (2.0%) participants developed stroke, 5103 (1.3%) participants developed dementia, and 2341 (0.6%) participants developed Parkinsonism. Nonlinear relationships were identified between SUA levels and stroke (J-shaped), dementia, and Parkinsonism (U-shaped). SUA levels of 4.2 mg/dl, 6.4 mg/dl, and 6.6 mg/dl yielded the lowest risk of stroke, dementia, and Parkinsonism, respectively. Besides, we found high SUA levels reduced the volumes of total brain, grey matter, white matter, grey matter in the hippocampus, and hippocampus, but increased lateral-ventricle volume. Inflammation accounted for 9.1% and 10.0% in the association of SUA with stroke and lateral-ventricle volume.
Conclusions: Lower SUA levels increased the risk of Parkinsonism, while both lower and higher SUA levels were positively associated with increased risk of stroke and dementia. Moreover, high SUA levels reduced brain structure volumes. Our findings suggest the association between SUA levels and brain-related disorders and highlight the importance of SUA management.

1. Introduction

Neurodegenerative diseases are characterized by progressive, selective loss of anatomically or physiologically related neuronal systems [1], including two aspects of acute (stroke, traumatic injuries) and chronic (such as Alzheimer's Disease, Parkinson's Disease, and multiple sclerosis) lesions [2]. Among them, stroke, dementia, and Parkinsonism are common subtypes that lead to high disability and death rates. With the global aging population, they cast increasing burdens on the healthcare system and society. Therefore, identifying individuals at high risk and preventing these neurodegenerative diseases are the major challenges ahead.

Uric acid (UA) is the final product of purine metabolism and the concentration of SUA should remain below 6.8 mg/dl in the body [3]. Excess SUA levels can lead to crystal deposits, inflammation, and tissue damage, and have been identified as a risk factor for cardiovascular metabolic and kidney diseases [4,5]. While studies showed an association between high SUA levels and stroke risk [6,7], debates persist regarding the dose-response relationship and potential sex differences. Conversely, too low SUA levels might be detrimental in some cases due to its

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antioxidant properties, which were thought to be neuroprotective. Studies reported an association between low SUA levels and an increased risk of dementia and Parkinson's disease [8,9]. These were mainly cross-sectional studies, while two large cohort studied reported conflicting results on SUA and dementia [10,11]. Cohort studies on SUA and Parkinson's Disease are scarce. Thus, more extensive longitudinal studies are needed to clarify the complex relationship between SUA and neurological degenerative disorders.

Neuroinflammation is a key factor in neurodegenerative diseases, which connect with chronic systemic inflammation [12]. UA has been identified as a trigger for inflammation related to the body's innate immune response [13]. However, whether inflammation mediates the association between SUA levels and neurological diseases remained unclear. To better illustrate the relationships between SUA levels and these aforementioned neurodegenerative diseases, we conducted our study on UK Biobank, a large-scale cohort study. We further explored the association of SUA levels with magnetic resonance imaging (MRI)-measured brain structures, which serve as important pathological structural changes and preclinical biomarkers of neurodegenerative disorders. Additionally, we explored the potential role of inflammation in the association of SUA with neurodegenerative diseases and changes in brain structure.

2. Methods

2.1. Study design and population

UK Biobank is a large-scale cohort study recruited over 500,000 participants aged 38–73 years between 2006 and 2010. Participants completed information on social-demographic characteristics, lifestyle, history of diseases and medications, biochemical tests, and genotype information. Individuals who were with hospital records before baseline or self-reported stroke, dementia, or Parkinsonism were excluded. Individuals with missing urate test results or covariate information were excluded. A total of 384,517 participants were included in the final prospective cohort analysis.

2.2. Exposure and outcomes

Blood samples were collected when participants attended the assessment center at baseline. Serum uric acid (SUA) was measured by uricase PAP analysis on Beckman Coulter AU5800 (Beckman Coulter). We converted SUA results as mg/dl in our analysis (1 mg/dl = 60 μmol/L).

Outcomes were neurodegenerative diseases including stroke, dementia, Parkinsonism, and multiple sclerosis. Onset time of stroke, dementia, and Parkinsonism was used based on the algorithmically defined outcomes in the UK Biobank. Algorithmically defined outcomes were calculated according to the section of self-reported illness, the International Classification of Diseased-9th and 10th version (ICD-9 and ICD-10). Stroke: ICD-9 codes (430.X, 431.X, 434.X, 434.0, 434.1, 434.9, and 436.X[5,6]), ICD-10 codes (I60, I61, I63, and I64.X[4]). Subtypes: ischaemic stroke (ICD-9: 434.X, 434.0, 434.1, 434.9, 436.X[5,6] and ICD-10: I63, I64.X[4]), intracerebral haemorrhage (ICD-9: 431.X and ICD-10: I61), subarachnoid haemorrhage (ICD-9: 430.X and ICD-10: I60). All cause dementia: ICD-9 (290.2–290.4, 291.2, 294.1, 331.0–331.2, and 331.5), ICD-10 (A81.0, F00, F01, F02, F03, F05.1, F10.6, G30, G31.0, G31.1, G31.8, and I67.3). Subtypes: Alzheimer's disease (ICD-9: 331.0 and ICD-10: F00, G30), vascular dementia (ICD-9: 290.4 and ICD-10: F01, I37.3), and frontotemporal dementia (ICD-9: 331.1 and ICD-10: F02.0, G31.0). All cause Parkinsonism: ICD-9 (3320, 3321, and 3330). Subtypes: Parkinson's disease (ICD-9: 3320 and ICD-10: G20), progressive supranuclear palsy (ICD-10: G23.1), and multiple system atrophy (ICD-10: G23.2, G23.3, and G90.3).

2.3. MRI imaging of brain structure

Magnetic resonance imaging (MRI) data were collected on a standard Siemens Skyra 3T with a standard Siemens 32-channel RF receive head coil. We used imaging-derived phenotypes (IDPs) provided by the UKB brain imaging team, and details of imaging acquisition protocols can be acquired at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id = 2367 and https://www.fmrib.ox.ac.uk/ukbiobank/protocol/. We assessed total brain, grey matter, white matter, grey matter in the hippocampus, hippocampus, lateral-ventricle, and total white matter hyperintensities (WMH) volumes. The WMH volume was ascertained by T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) images, and the others were on T1 structural brain MRI. Grey matter and white matter volumes were normalized for head size, and the total brain volume was the sum of these two volumes. Grey matter in the hippocampus, hippocampus, lateral-ventricle, and WMH volumes were normalized by multiplying the volumetric scaling from the T1 head image to standard space. The WMH volume was additional log-transformed.

2.4. Covariates

The following covariates were considered: age (continuous), sex (male/female), ethnicity (White, Mixed, Asian, Black, and others), education (college or university/none college or university), Townsend deprivation index (TDI) (continuous), smoking status (never/former/current), alcohol intake status (never/former/current), physical activity (continuous, summed MET minutes/week for all activity), healthy diet score, serum high-density lipoprotein (HDL) (continuous), serum low-density lipoprotein (LDL) (continuous), serum triglycerides (TG) (continuous), serum total cholesterol (TC) (continuous), renal function (normal/abnormal), diabetes (yes/no), cardiovascular diseases (CAD) (including hypertension, coronary heart diseases, heart failure, arrhythmia, atrial fibrillation, or stroke, yes/no), urate-lowering therapy (yes/no), and body mass index (BMI) (continuous). The healthy diet score was calculated as follows: vegetable intake $\geq$4 tablespoons each day; fruit intake $\geq$3 pieces each day; fish intake $\geq$2 each week; unprocessed red meat intake $\leq$2 each week; and processed meat intake $\leq$2 each week. A healthy diet score was calculated by assigning 1 point for each criterion that was met. The total score for a healthy diet was 5. Glomerular filtration rate (eGFR) was ascertained on serum creatinine and cystatin C as reported [14], and exceeding 90 ml/min was thought normal.

2.5. Statistical analyses

Follow-up time was counted from the time they entered the UK Biobank cohort until the onset of the neurodegenerative diseases (including their subtypes), or until their death as recorded in the death register (Field ID: 40000), or November 30, 2021.

Baseline characteristics of the study population were expressed by medians and quartiles for asymmetric distribution of continuous variables and counts and percentages for categorical variables. Comparison among characteristics of individuals with or without hyperuricemia was performed through t-testes or Mann-Whitney U test for continuous variables and chi-squared tests for categorical variables. Restricted cubic spline (RCS) models were used to evaluate the nonlinear association between continuous SUA levels and neurodegenerative diseases, with 5 knots at the 5th, 27.5th, 50th, 72.5th, and 95th centiles. Cox proportional hazard models were used to analyze the association between SUA categories and disease onset, and Schoenfeld's residuals test was used. Besides SUA levels and SUA categories, both restricted cubic spline models and Cox regression models were adjusted for age, sex, ethnicity, education, TDI, smoking status, alcohol intake status, physical activity, healthy diet scores, TC, TG, LDL, HDL, renal function, history of diabetes, history of CAD, use of urate-lowering therapy, and BMI. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in the above models. To explore the association between SUA levels and MRI-ascertained brain structures, we used 5 knots' RCS analyses based on multiple linear regression.

Mediation analyses were performed to evaluate the effect of inflammation in the association of SUA with outcomes of

neurodegenerative disease and results of MRI-ascertained brain structure, respectively. Inflammation was assessed by low-grade chronic inflammation (INFLA) score, which was a composite index calculated by C-reactive protein (CRP), white blood cell (WBC), platelet count, and neutrophil-to-lymphocyte ratio (NLR) [15]. Mediation analysis models were adjusted for the same aforementioned covariates.

Subgroup analyses were performed on gender (male or female) and age (≥60 or <60), and interaction analysis was used to test the interaction between SUA and these factors. Sensitivity analyses were performed by excluding participants with outcomes or death onset in the first 2 years of follow-up or those taking medications that interfere with serum uric acid level in long-term oral administration (Listed in Supplementary Table S1). Taking death as a competing risk into consideration, we used Fine and Grey's competing risk models to reassess the robustness of the study results. Two-sided hypothesis tests were used, and the significance was considered as P 0.05. All statistical analyses were performed using SPSS version 16.0 and R version 4.3.1.

3. Results

3.1. Baseline characteristics

After excluding individuals without urate test results and main covariates, 384,517 participants were included in the cohort. Table 1 presents the baseline characteristics of the inclusive population. Individuals with higher SUA had higher serum TG, BMI, incidence of CAD, incidence of diabetes, frequency of smoking, frequency of drinking, and lower education, healthy diet scores, physical activity, serum HDL, and eGFR.

During the median follow-up time of 12.8 years (interquartile range [IQR]:12.0, 13.5) for diseases onset, 7821 (2.0%) participants had stroke [6209 ischaemic stroke (IS), 1310 intracerebral haemorrhage (ICH), and 786 subarachnoid haemorrhage (SAH)], 5103 (1.3%) participants developed dementia [2244 Alzheimer's disease (AD), 1018 vascular dementia (VaD), and 177 frontotemporal dementia (FTD)], 2341 (0.6%) participants had parkinsonism [2099 Parkinson's disease (PD), 115 progressive supranuclear palsy (PSP), and 74 multiple system atrophy (MSA)].

3.2. Nonlinear associations between serum uric acid levels and neurodegenerative diseases

We used restricted cubic spline (RCS) analysis to explore the relationships between SUA levels and stroke, dementia, and Parkinsonism. In multivariable models, SUA levels displayed a nonlinear association between stroke, dementia, and Parkinsonism (P for nonlinear < 0.05) (Fig. 1). SUA levels showed a J-shaped association with stroke and a U-shaped association with dementia and Parkinsonism (Fig. 1). The SUA level of 4.2 mg/dl showed the lowest hazard ratio for stroke, while SUA levels of 6.2 and 6.6 mg/dl were identified as the lowest HRs for dementia and Parkinsonism (Fig. 1). U-shaped associations were found in 4 subtypes of ICH, AD, VaD, and PD, but not in the other subtypes (FTD, PSP, and MSA) (Supplementary Fig. S1). While the risk of IS increased with SUA levels (Supplementary Fig. S1).

3.3. Risk of different serum uric acid levels and neurodegenerative diseases

To analyze the association between different SUA levels and the risk of neurodegenerative diseases, we defined SUA to 6 levels according to the 5

Table 1
Baseline characteristics of the study population with different SUA levels.

Characteristics	Participants, No. (%)			
	Total	Without hyperuricemia	With hyperuricemia	P value
Sex, n (%)				<0.001
Men	175,827 (45.7)	146,014 (42.3)	29,813 (76.4)	
Women	208,690 (54.3)	199,491 (57.7)	9199 (23.6)	
Age, median (IQR)	58.0 (50.0,63.0)	58.0 (50.0,63.0)	58.0 (51.0,64.0)	<0.001
Race, n (%)				<0.001
White	366,810 (95.4)	329,702 (95.4)	37,108 (95.1)	
Mixed	2185 (0.6)	1973 (0.6)	212 (0.5)	
Asian	7375 (1.9)	6577 (1.9)	798 (2.0)	
Black	5127 (1.3)	4527 (1.3)	600 (1.5)	
Others	3020 (0.8)	2726 (0.8)	294 (0.8)	
Education, n (%)				<0.001
University/college	129,109 (33.6)	117,526 (34.0)	11,583 (29.7)	
Non university/college	255,408 (66.4)	227,979 (66.0)	27,429 (70.3)	
TDI, median (IQR)	−2.2 (−3.7,0.3)	−2.2 (−3.7,0.3)	−2.0 (−3.6,0.8)	<0.001
Smoking status, n (%)				<0.001
Never	211,427 (55.0)	193,287 (55.9)	18,140 (46.5)	
Former	39,254 (10.2)	35,491 (10.3)	3763 (9.6)	
Current	133,836 (34.8)	116,727 (33.8)	17,109 (43.9)	
Alcohol intake, n (%)				<0.001
Never	28,507 (7.4)	26,188 (7.6)	2319 (5.9)	
Former	275,735 (71.7)	249,947 (72.3)	25,788 (66.1)	
Current	80,275 (20.9)	69,370 (20.1)	10,905 (28.0)	
MET-minute/week, median (IQR)	2346.0 (990.0,3066.0)	2373.0 (1004.0,3066.0)	2079.5 (822.0,2844.0)	<0.001
Healthy diet score, mean ± SD	3.0 ± 1.2	3.0 ± 1.2	2.7 ± 1.2	<0.001
TC, median (IQR), mmol/L	5.7 (4.9,6.4)	5.7 (4.9, 6.4)	5.6 (4.8,6.4)	<0.001
TG, median (IQR), mmol/L	1.5 (1.0,2.1)	1.4 (1.0,2.1)	2.0 (1.4,2.9)	<0.001
HDL, median (IQR), mmol/L	1.4 (1.2,1.7)	1.4 (1.2,1.7)	1.2 (1.0,1.4)	<0.001
LDL, median (IQR), mmol/L	3.5 (3.0,4.1)	3.5 (3.0,4.1)	3.6 (2.9,4.2)	<0.001
eGFR, median (IQR), mL/min/1.73 m^2	96.3 (86.2,105.7)	97.2 (87.4,106.3)	87.5 (76.2,98.0)	<0.001
BMI, median (IQR)	26.7 (24.1,29.8)	26.4 (23.9, 29.3)	29.7 (27.1,33.0)	<0.001
Diabetes, n (%)	15,403 (4.0)	12,839 (3.7)	2564 (6.6)	<0.001
CAD, n (%)	108,913 (28.3)	8984 (26.0)	19,229 (49.3)	<0.001
Urate-lowering therapy, n (%)	4309 (1.1)	3537 (1.0)	772 (2.0)	<0.001
INFLA-score, mean ± SD	0.0 ± 6.1	0.2 ± 6.1	1.6 ± 6.0	<0.001

Hyperuricemia: serum urate levels >7.0 mg/dl for males and >6.8 mg/dl for females (>7.0 mg/dl for postmenopausal women).

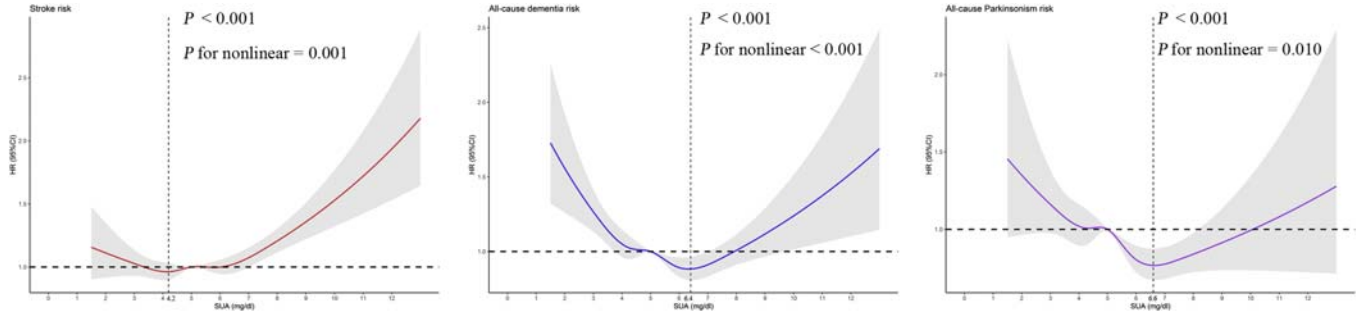

Fig. 1. Restricted cubic spine models for the association between SUA levels and stroke, dementia, and Parkinsonism. Models were adjusted for sex, age, ethnicity, education, TDI, smoking status, alcohol intake status, physical activity, healthy diet scores, serum TC, TG, HDL, LDL, renal function, diabetes, CAD, use of urate-lowering therapy, and BMI.

knots of RCS analyses (categorized separately for males and females). We compared each level with the lowest risk range of stroke, dementia, and Parkinsonism (Table 2 and Supplementary Fig. S2). In the multivariable-adjusted models, individuals with SUA interval of $\geq 95^{th}$ were at 1.34(1.22–1.48) higher risk of stroke. For subtypes of stroke, individuals with SUA levels of $\geq 95^{th}$ were also found at 1.33 (1.19–1.49) and 1.65(1.29–2.11) higher risk of IS and ICH, respectively. Individuals with SUA interval of 72.5^{th}–95^{th} were at the lowest risk of dementia, while SUA levels below 27.5^{th} and $\geq 95^{th}$ showed relatively higher risk compared to it. In subtypes of dementia, individuals with SUA levels below 50^{th} had a higher risk of AD. While both SUA levels below 27.5^{th} and $\geq 95^{th}$ had a higher risk of VaD (1.49, 1.11–2.01; 1.34, 1.11–1.63 and 1.60, 1.18–2.18, respectively). For Parkinsonism, higher HRs were observed in individuals with SUA levels of 0–5^{th}, 5^{th}–27.5^{th}, and 27.5^{th}–50^{th} (1.47, 1.21−1.79; 1.26, 1.10−1.43 and 1.21, 1.06−1.37, respectively). In PD, individuals with the above same SUA levels all displayed higher HRs (1.45, 1.17–1.79; 1.29, 1.12–1.48 and 1.22, 1.07–1.39, respectively), while no significant differences were found across other SUA levels. There was no significant difference in HRs across any SUA levels for PSP and MSA.

3.4. Associations of serum uric acid levels with brain imaging structures

We further explored the relationship between SUA levels and brain imaging structures (Fig. 2). In both sex and age-adjusted and multivariable models, SUA levels showed a U-shaped association with lateral ventricle volume, and an inverted U-shaped association with total brain, grey matter, and hippocampus volumes (all *P* for nonlinear <0.05) (Fig. 2 and Supplementary Fig. S3). The volumes of total brain, grey matter, and hippocampus were higher at SUA levels of 4−6 mg/dl, while the lateral ventricle volume was lower in this SUA range. No nonlinear relationships were observed in white matter volume or grey matter volume in the hippocampus (*P* for nonlinear >0.05) (Fig. 2 and Supplementary Fig. S3). Although the volume of WMH displayed a nonlinear relationship with SUA levels when adjusted for only age and sex, the nonlinear relationship was not found after adjusting for multiple covariates.

3.5. Mediation analyses

The mediating effect of inflammation was found in the association of SUA with stroke and lateral ventricle volume, with significant

Table 2
Multivariable-adjusted Cox regression of SUA levels and stroke, dementia, and Parkinsonism.

SUA[c]	Sample size	Events, n (%)	Sex and age-adjusted model [a]		Multivariate-adjusted model [b]	
			HR (95% CI)	P value	HR (95% CI)	P value
Stroke						
–5^{th}	19,239	375 (1.9)	1.19 (1.06−1.33)	0.003	1.13 (1.01−1.27)	0.032
5^{th}– 27.5^{th}	86,387	1,473 (1.7)	1.00 (Reference)		1.00 (Reference)	
27.5^{th}– 50^{th}	86,671	1,559 (1.8)	1.02 (0.95−1.09)	0.653	1.00 (0.93−1.07)	0.985
50^{th}– 72.5^{th}	86,489	1,760 (2.0)	1.11 (1.03−1.19)	0.004	1.05 (0.98−1.12)	0.207
72.5^{th}– 95^{th}	86,502	1,977 (2.3)	1.19 (1.11−1.27)	<0.001	1.04 (0.97−1.12)	0.244
95^{th}–	19,229	677 (3.5)	1.77 (1.62−1.94)	<0.001	1.34 (1.22−1.48)	<0.001
All-cause dementia						
–5^{th}	19,239	277 (1.4)	1.34 (1.17−1.52)	<0.001	1.30 (1.14−1.50)	<0.001
5^{th}– 27.5^{th}	86,387	1,113 (1.3)	1.13 (1.04−1.23)	0.003	1.18 (1.08−1.29)	<0.001
27.5^{th}– 50^{th}	86,671	1,078 (1.2)	1.02 (0.94−1.11)	0.652	1.08 (0.99−1.17)	0.080
50^{th}– 72.5^{th}	86,489	1,044 (1.2)	0.93 (0.85−1.01)	0.066	0.96 (0.89−1.05)	0.383
72.5^{th}– 95^{th}	86,502	1,222 (1.4)	1.00 (Reference)		1.00 (Reference)	
95^{th}–	19,229	369 (1.9)	1.26 (1.12−1.41)	<0.001	1.13 (1.01−1.27)	0.039
All-cause Parkinsonism						
–5^{th}	19,239	137 (0.7)	1.47 (1.21−1.77)	<0.001	1.47 (1.21−1.79)	<0.001
5^{th}– 27.5^{th}	86,387	528 (0.6)	1.21 (1.07−1.37)	0.002	1.26 (1.10−1.43)	0.001
27.5^{th}– 50^{th}	86,671	529 (0.6)	1.16 (1.03−1.31)	0.018	1.21 (1.06−1.37)	0.003
50^{th}– 72.5^{th}	86,489	506 (0.6)	1.06 (0.94−1.20)	0.373	1.09 (0.96−1.24)	0.172
72.5^{th}– 95^{th}	86,502	504 (0.6)	1.00 (Reference)		1.00 (Reference)	
95^{th}–	19,229	137 (0.7)	1.16 (0.96−1.41)	0.116	1.08 (0.89−1.31)	0.420

[a] Models were adjusted for sex and age.
[b] Models were adjusted for sex, age, ethnicity, education, TDI, smoking status, alcohol intake status, physical activity, healthy diet scores, serum TC, TG, HDL, LDL, renal function, diabetes, CAD, use of urate-lowering therapy, and BMI.
[c] 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} cut-off values of SUA level were 4.1 mg/dl, 5.2 mg/dl, 5.8 mg/dl, 6.5 mg/dl, and 8.0 mg/dl for males and 2.9 mg/dl, 3.8 mg/dl, 4.4 mg/dl, 5.0 mg/dl, and 6.5 mg/dl for females.

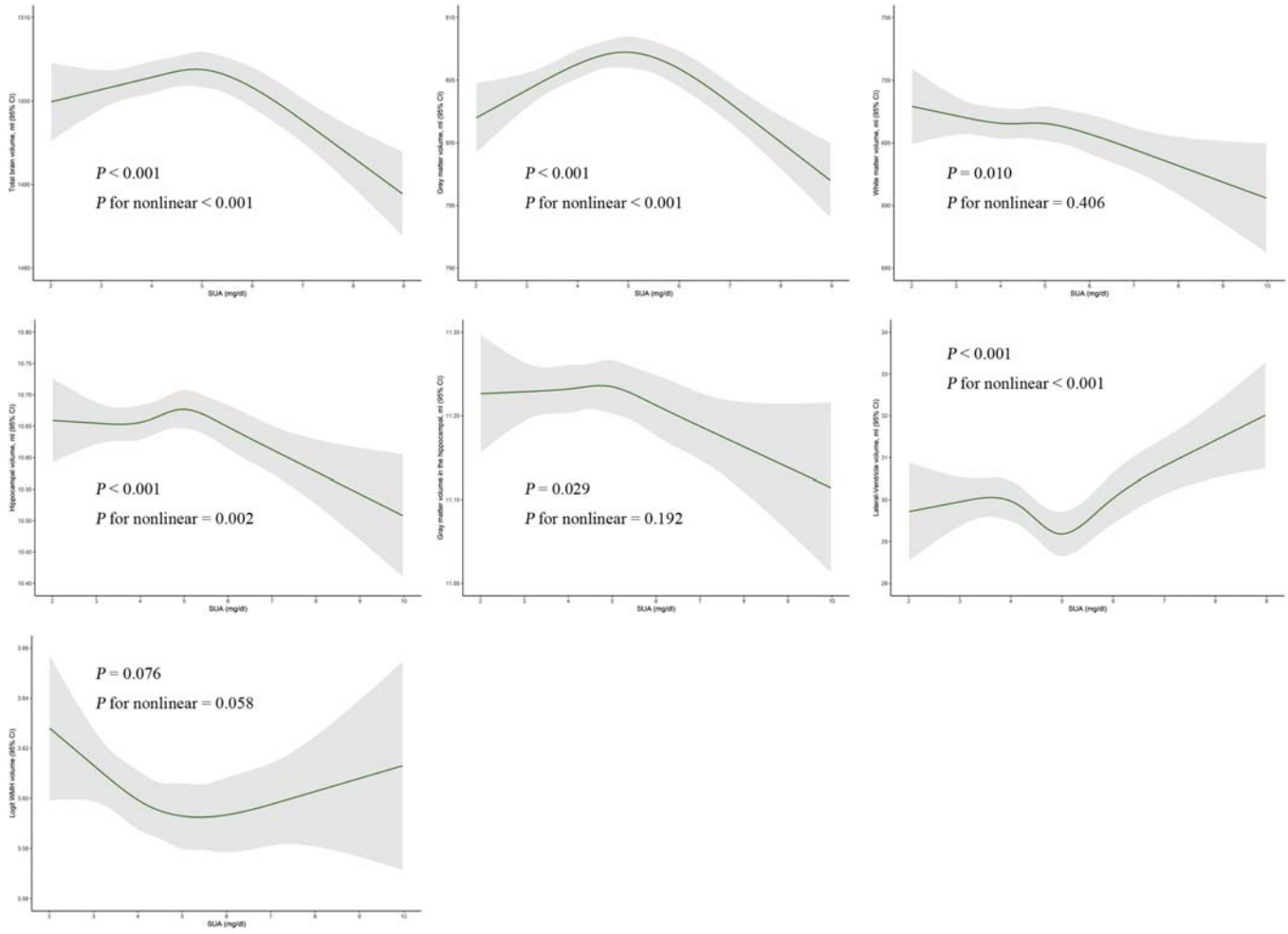

Fig. 2. Restricted cubic spine models for the association between SUA levels and total brain, grey matter, white matter, hippocampus, grey matter in the hippocampus, lateral-ventricle, and total white matter hyperintensities (WMH) volumes. Models were adjusted for sex, age, ethnicity, education, TDI, smoking status, alcohol intake status, physical activity, healthy diet scores, serum TC, TG, HDL, LDL, renal function, diabetes, CAD, use of urate-lowering therapy, and BMI.

intermediate ratios of 9.1% and 10.0% (Supplementary Fig. S4 and Table S2). Inflammation could not account for the association of SUA with dementia, Parkinsonism, or other MRI-ascertained brain structures.

3.6. Subgroup and sensitivity analyses

In the stratified analysis of sex, similar results were obtained in both males and females for stroke (*P* for interaction = 0.927), dementia (*P* for interaction = 0.790), and Parkinsonism (*P* for interaction = 0.539) (Supplementary Tables S3, S4 and S5). Similar results were also obtained on age for stroke (*P* for interaction = 0.163) (Supplementary Table S6). The risk of dementia and Parkinsonism varied with age (both *P* for interaction = 0.027) (Supplementary Tables S7 and S8). Individuals aged ≥60 years old had a higher HR of dementia only when SUA levels were below the 27.5th, while a higher risk of Parkinsonism was only observed in individuals aged <60 years old when SUA levels were below the 5th.

After excluding participants with follow-up time <2 years or those taking medications that interfere with SUA levels in long-term oral administration, the results remained consistent with the initial analyses (Supplementary Tables S9 and S10). The results were the same when utilizing Fine-Gray's competing risk models (Supplementary Table S11).

4. Discussion

In this large-scale prospective cohort study involving more than 300,000 participants, we identified nonlinear relationships between SUA levels and stroke (J-shaped), dementia, and Parkinsonism (U-shaped). SUA levels of 4.2 mg/dl, 6.4 mg/dl, and 6.6 mg/dl yielded the lowest risk of stroke, dementia, and Parkinsonism, respectively. Lower SUA levels increased the risk of Parkinsonism, while both lower and higher SUA levels were positively associated with increased risk of stroke and dementia. Furthermore, we found high SUA levels were associated with reduced volumes of total brain, grey matter, white matter, grey matter in the hippocampus, and hippocampus while increasing lateral ventricle volume. Chronic low-grade inflammation partially mediated the association of SUA with stroke and the change in lateral-ventricle volume.

The association between high SUA levels and an increased risk of stroke has been consistently demonstrated in observational studies [6]. The URRAH study [16] identified the cut-off value of 4.79 mg/dL for SUA in the prognostic of cerebrovascular (CBV) events through Receiver Operation Characteristic (ROC), our time-to-event analysis found that individuals with SUA levels of 4.2 mg/dL were at the lowest risk of stroke, which was close to the finding. Research on different regions and sample sizes might yield different results. The URRAH study was conducted in Italian with a much smaller sample size of 14,588 participants and might draw different results. Our research further confirmed this relationship regardless of sex and age. A meta-analysis of 13 prospective studies indicated a consistent relationship between SUA levels and stroke across both genders [17], which our study positively supported. We also observed similar trends with age, as stroke risk increases with SUA levels in individuals both over and under 60 years old. Additionally, while a prospective cohort study [18] reported an association between high SUA

levels and the risk of hemorrhagic stroke but not ischemic stroke, our study revealed a U-shaped relationship between SUA levels and ICH and a significantly increased risk of ICH under higher SUA conditions.

The Rotterdam Study [10] involving more than 5000 participants discovered that higher SUA levels were associated with a decreased risk of dementia and improved cognitive function. Two separate cohorts [19,20] revealed that individuals with gout had a lower risk of developing AD and vascular dementia compared to those without gout. Our study uncovered a U-shaped relationship between SUA levels and dementia. We found that individuals in the top 5th and below 27.5th SUA levels were associated with an increased risk of dementia. Similar trends were observed for VaD, while SUA below the 50th of the population displayed a higher risk of AD. Women showed higher susceptibility to dementia than men [21], our subgroup analysis found the association between SUA levels and dementia risk remained almost consistent across genders, with women only displaying higher dementia risk under lower SUA conditions. Age was recognized as another risk factor for dementia [22], we found individuals under 60 years old showed increased susceptibility under high SUA conditions.

The relationship between SUA levels and Parkinsonism is complex. While low SUA levels were associated with an increased risk of PD [23], the association between high SUA levels and Parkinsonism remains uncertain. Some large cohort studies [24,25] suggested a positive connection between high SUA levels and Parkinsonism, showing a lower risk of PD in gout patients. However, a retrospective cohort [26] of over 300,000 participants in Korea and a meta-analysis [27] suggested no association between gout and an increased risk of PD. Our study revealed a nonlinear relationship between SUA levels and Parkinsonism, with SUA levels of 6−7 mg/dl at a relatively lower risk of Parkinsonism.

Clinical studies indicated an association between high SUA levels and increased risk of stroke, but the mechanism was currently unclassified. Our study revealed the pro-inflammatory effect of UA might partially mediate the association with stroke. Research has reported a higher concentration of UA in humans' atherosclerotic plaque [28], which might lead to localized chronic inflammation in vascular smooth muscle cells, increase platelet adhesiveness, and promote thrombus formation [29]. Decreased levels of SUA increased the risk of developing dementia and Parkinsonism, which might potentially be due to the decline of the brain's antioxidant capacity [30,31] and exacerbated local oxidative stress. Additionally, we found that high SUA levels were associated with changes in brain structure, which had not been reported yet. Consistent with reduced volumes of total brain [32], grey matter [33], white matter [34], and hippocampus [35] in dementia, we found high SUA levels reduced the volumes of these brain structure. Notably, we also found that elevated SUA levels were associated with an increase in lateral ventricle volume, which was a distinguishing feature in dementia [36]. These findings suggested these brain structural abnormalities might be a contributing factor in the exacerbation of dementia under high SUA level conditions. And we found chronic inflammation related to SUA might explain the change in lateral ventricle volume. However, our study did not find evidence of inflammation mediating the relationship between SUA and dementia. Further research can be conducted to elucidate the interplay between SUA and dementia.

5. Limitations

Our study has two strengths of large sample size and well-adjusted on multiple factors. However, our study also has several limitations. Firstly, we conducted research on the one serum urate test at the first time of cohort attendance, and participants were not required to fast before collecting blood samples. Although fasting might not have a significant influence on serum uric acid on laboratory tests [37], we still could not rule out the influence of fasting and the urate results may be biased. Secondly, participants' health conditions and social status might change during the long-term follow-up. We cannot ignore the possibility of these health changes due to the lack of updated information. Lastly, most participants of the UK Biobank were white British, though we adjusted for ethnicity in the analysis, our findings might have some kind of regional and ethnic representation and need more evidence support from multi-region research worldwide.

6. Conclusions

In our large-scale population cohort study of the UK Biobank, we found that lower SUA levels increased the risk of Parkinsonism, while both lower and higher SUA levels were positively associated with increased risk of stroke and dementia. Moreover, we found that high SUA levels reduced volumes of total brain, grey matter, white matter, grey matter in the hippocampus, and hippocampus volumes, but increased lateral-ventricle volume. Chronic inflammation partially mediated the association of SUA with stroke and lateral-ventricle volume. Our findings support the association between SUA levels and neurodegenerative diseases and highlight the importance of SUA management. Predictive models and early prevention can be implemented for the populations with high-risk SUA levels for long-term health.

Ethics approval and consent to participate

All UK Biobank participants provided informed consent and the UK Biobank gained approval from the Northwest Multi-centre Research Ethics Committee (MREC) (REC reference: 21/NW/0157). This research was conducted using UK Biobank under application number 90369.

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Author contributions

XZ, YL, ZJ, and JC designed the study. ZJ, JC, and SW acquired, analyzed, and interpreted the data. ZJ and HK drafted the manuscript. ZJ, SW, SJ, and JC completed the statistical analysis. XZ and YL supervised the final manuscript. WF, ZL and JL conducted the validation. JC and CW made critical revision of the manuscript. XZ and Y L had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZJ and JC contributed equally to the article.

Conflicts of interest

The authors declare that the research does not have any commercial or financial conflicts of interest related to the publication of this paper and have signed their consent for publishing the article. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

Data supporting the findings of this article can be accessed by approved researchers through application to UK Biobank (ukbiobank.ac.uk/enable-your-research).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100319.

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