Research Square

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Associations of serum uric acid, renal function, and intermittent hypoxemia with post-stroke cognitive impairment and physical frailty in older adults with ischemic stroke: a retrospective cross-sectional study

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Abstract

Background

Post-stroke cognitive impairment (PSCI) is common in older adults with ischemic stroke. The association between serum uric acid (SUA) and cognition remains uncertain and may depend on renal function and sleep-related hypoxemia. We examined associations of SUA with renal function, sleep-disordered breathing, cognition, and physical frailty.

Methods

This single-center retrospective cross-sectional study included 500 patients aged ≥ 60 years hospitalized between January 2023 and January 2026. Clinical data, laboratory measures, overnight polysomnography, and geriatric assessments were collected. PSCI was defined as an education-adjusted Montreal Cognitive Assessment score < 26, and physical frailty was assessed using the Fried phenotype. SUA was analyzed per 1-standard-deviation (SD) increase and by sex-specific tertiles. Multivariable linear and logistic regression, progressively adjusted cognitive models including estimated glomerular filtration rate (eGFR) and oxygen desaturation index (ODI), restricted cubic splines, and frailty sensitivity analyses were used.

Results

Among 500 participants, 230 (46.0%) had PSCI. Each 1-SD increase in SUA was associated with lower eGFR (β=-5.78 mL/min/1.73 m²; 95% CI, -6.60 to -4.97) and higher ODI (β = 4.50 events/h; 95% CI, 3.69 to 5.31). In the fully adjusted cognitive model, higher SUA remained associated with a lower MoCA score (β=-0.43; 95% CI, -0.63 to -0.24) and higher odds of PSCI (OR = 1.75; 95% CI, 1.26 to 2.43), although estimates were attenuated after adjustment for eGFR and ODI. Compared with the lowest SUA tertile, the highest tertile was associated with a lower MoCA score (β=-0.86; 95% CI, -1.25 to -0.46) and higher odds of PSCI (OR = 2.41; 95% CI, 1.22 to 4.76). Spline analyses showed significant overall associations with both cognitive outcomes (both $P < 0.001$) but no significant nonlinearity (MoCA, $P = 0.073$; PSCI, $P = 0.157$). Higher SUA and ODI and lower eGFR and minimum SpO_2 were also associated with physical frailty.

Conclusions

Higher SUA was associated with poorer renal function, greater sleep-related hypoxemia, poorer cognition, and physical frailty in older adults with ischemic stroke. Attenuation of the SUA-cognition associations after adjustment for eGFR and ODI suggests shared variation rather than established

mediation. Multicenter prospective studies are needed to clarify temporal relationships and clinical utility.

1.Background

Post-stroke cognitive impairment (PSCI) is a common and clinically important complication of ischemic stroke. Its manifestations range from mild cognitive decline to post-stroke dementia and may involve attention, executive function, memory, language, and visuospatial abilities [1, 2]. A substantial proportion of stroke survivors develop cognitive impairment during the early post-stroke period or subsequent follow-up, and older age, lower cognitive reserve, greater stroke severity, previous cerebrovascular injury, and coexisting cerebral small-vessel disease have all been associated with increased susceptibility [1–3]. In older adults, cognitive impairment can adversely affect disease self-management, participation in rehabilitation, and treatment adherence and is associated with functional dependence, recurrent stroke, and unfavorable long-term functional outcomes [1, 4]. Identifying clinically accessible markers with plausible biological relevance may therefore help refine cognitive risk stratification and comprehensive care in older adults with ischemic stroke.

Serum uric acid (SUA), the end product of purine metabolism in humans, has a complex relationship with neurocognitive function. Uric acid is an important circulating antioxidant; however, persistently elevated SUA may also be associated with oxidative stress, inflammation, endothelial dysfunction, and vascular injury [5]. Studies in stroke populations have linked higher SUA to poorer cognitive performance [6], whereas other work has suggested potential nonlinear and sex-specific associations between SUA and PSCI [7]. These inconsistencies indicate that SUA should not be interpreted independently of its metabolic and organ-function context. Uric acid is primarily handled by the kidneys through filtration, reabsorption, secretion, and excretion; consequently, impaired renal function can influence circulating SUA and is itself associated with cognitive impairment. Previous studies have suggested that estimated glomerular filtration rate (eGFR) may modify the association between SUA and post-stroke cognitive performance and that the SUA-to-serum creatinine (SUA/SCr) ratio may provide information beyond SUA alone by partly accounting for renal clearance [6, 8, 9]. Concurrent assessment of eGFR, SCr, and cystatin C may therefore provide a more informative renal context for interpreting the association between SUA and cognition after stroke.

Sleep-disordered breathing (SDB) is another common and often underrecognized abnormality in patients with stroke. A meta-analysis showed a high prevalence of SDB after stroke or transient ischemic attack, with abnormalities persisting across different stages of stroke recovery [10]. Recurrent apnea and hypopnea can produce sleep fragmentation and intermittent hypoxia, accompanied by oxidative stress, inflammation, sympathetic activation, endothelial dysfunction, and impaired cerebrovascular regulation, all of which may be relevant to cognitive impairment [11]. The apnea-hypopnea index (AHI) mainly captures the frequency of respiratory events, whereas the oxygen desaturation index (ODI), the percentage of total sleep time with peripheral oxygen saturation < 90% (T90), and minimum SpO_2

characterize different aspects of nocturnal hypoxemic exposure. Recent evidence suggests that quantifying the frequency, depth, and duration of hypoxemia may provide information relevant to cognition beyond AHI alone [12]. Cognitive impairment and physical frailty also frequently coexist in older stroke populations; prior stroke cohorts have linked both physical and brain frailty to adverse cognitive and functional outcomes [13]. Together, these observations suggest that urate metabolism, renal function, sleep-related respiratory physiology, and cognitive and physical vulnerability may represent interconnected rather than isolated clinical dimensions.

Most previous studies have examined SUA and cognition, renal function and cognition, or SDB and cognition separately. Few have integrated SUA, renal indices, standard overnight polysomnographic measures, cognitive performance, and physical frailty within the same population of older adults with ischemic stroke. In particular, it remains unclear whether SUA is associated with MoCA performance and PSCI after comprehensive adjustment for demographic characteristics, vascular risk factors, stroke severity, relevant medications, and depressive symptoms, and how these associations change after further accounting for renal function and intermittent hypoxemia. We therefore aimed to: (1) evaluate the associations of SUA with renal function and multidimensional sleep-respiratory measures; (2) examine linear and potential nonlinear associations of SUA with education-adjusted MoCA scores and PSCI; (3) characterize changes in the SUA-cognition effect estimates after sequential adjustment for eGFR and ODI; and (4) further examine the associations of SUA, eGFR, and nocturnal hypoxemia with physical frailty. Given the retrospective cross-sectional design, all findings were interpreted as observational associations and not as evidence of causality or formal mediation.

2.Methods

2.1 Study design and participants

This was a single-center retrospective cross-sectional study. We consecutively screened patients with ischemic stroke who were hospitalized in the Department of Neurology, Affiliated Hospital of Yangzhou University, between January 2023 and January 2026. Ischemic stroke was diagnosed on the basis of clinical neurological deficits in conjunction with cranial computed tomography or magnetic resonance imaging findings.

The inclusion criteria were: (1) age ≥ 60 years; (2) a diagnosis of ischemic stroke; (3) complete measurements of SUA and renal function; (4) completion of technically adequate standard overnight polysomnography (PSG); (5) completion of cognitive, physical frailty, and activities-of-daily-living assessments; and (6) availability of the main clinical data. Patients were excluded if they were aged < 60 years; had missing or technically inadequate PSG data; had missing or incomplete MoCA assessments; had missing SUA or renal-function data; had a previous diagnosis of dementia, Alzheimer disease, dementia with Lewy bodies, or another neuropsychiatric disorder likely to substantially affect cognition; or were unable to complete the required assessments because of severe aphasia, impaired

consciousness, or marked hearing or visual impairment. The participant selection process is shown in Fig. 1.

2.2 Clinical data and laboratory measurements

Demographic and clinical data were obtained from the electronic medical record, including age, sex, years of education, height, weight, body mass index (BMI), current smoking and drinking status, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, and previous stroke. We recorded the National Institutes of Health Stroke Scale (NIHSS) score at admission and the prestroke modified Rankin Scale (mRS) score. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9), with higher scores indicating greater symptom severity [14]. Use of urate-lowering medications, diuretics, and sedative-hypnotics was also recorded.

SUA, serum creatinine (SCr), blood urea nitrogen (BUN), and cystatin C were measured from the first fasting morning blood sample obtained within 24 hours after admission. eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation without a race coefficient [15]. The SUA/SCr ratio was calculated from contemporaneous SUA and SCr measurements.

2.3 Polysomnography

Once vital signs and neurological status were relatively stable, patients underwent standard overnight PSG during hospitalization, generally within 7 days of admission. Recordings were acquired using the SOMNOmedics V6 system (SOMNOmedics GmbH, Germany). Electroencephalographic electrodes were positioned according to the international 10–20 system [16], with simultaneous recording of electro-oculography, chin electromyography, electrocardiography, oronasal airflow, thoracoabdominal respiratory movements, and pulse oximetry.

During data preparation, all raw PSG recordings were re-reviewed and scored by two uniformly trained professionals according to version 3 of the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events [17]. Disagreements were resolved by review by a third trained professional.

Sleep variables included total sleep time, sleep efficiency, percentage of stage N3 sleep, percentage of rapid eye movement (REM) sleep, arousal index, AHI, ODI, T90, mean SpO_2, and minimum SpO_2. Moderate-to-severe SDB was defined as AHI ≥ 15 events/h. ODI was defined as the number of events per hour of sleep in which SpO_2 decreased by ≥ 3%.

2.4 Cognitive assessment

Cognitive function was assessed using the Chinese version of the Montreal Cognitive Assessment (MoCA) [18]. Assessments were conducted by uniformly trained investigators during hospitalization when patients were alert and their vital signs and neurological status were relatively stable. The MoCA is scored from 0 to 30, with higher scores indicating better cognitive performance. One point was added for

participants with ≤ 12 years of education, with the education-adjusted total capped at 30. The education-adjusted MoCA score was analyzed as a continuous cognitive outcome, and PSCI was defined as an education-adjusted MoCA score < 26 [18].

2.5 Physical frailty and activities of daily living

Physical frailty was assessed using the Fried frailty phenotype, comprising five components: unintentional weight loss, exhaustion, low physical activity, slow walking speed, and weak grip strength [19]. Unintentional weight loss, exhaustion, and physical activity were assessed using standardized questioning and medical-record information. Walking speed and grip strength were assessed using standardized walking and grip-strength tests and classified according to the relevant sex-, height-, or BMI-specific thresholds.

Each component was scored as 1 point when present, yielding a total score of 0–5. A score of 0 indicated robustness, 1–2 prefrailty, and ≥ 3 physical frailty. Activities of daily living were assessed using the 100-point Barthel Index, with higher scores indicating greater independence [20].

2.6 Exposure and study outcomes

The primary exposure was SUA. SUA was analyzed as a continuous variable, per 1-sample-SD increase, and as a categorical variable. The sample SD of SUA was 70.9 μmol/L.

Given physiological sex differences in SUA distributions, tertile cut points were calculated separately in women and men, and participants were then combined into corresponding T1, T2, and T3 categories. The cut points were 340.2 and 394.7 μmol/L in women and 374.2 and 431.9 μmol/L in men.

The primary study outcomes were the education-adjusted continuous MoCA score and binary PSCI status; physical frailty was a secondary outcome. eGFR and ODI were selected as key markers of renal function and intermittent hypoxemia, respectively, to characterize how the SUA-cognition associations changed when these dimensions were sequentially included in the models.

For analyses reporting standardized effect estimates, SUA, eGFR, cystatin C, ODI, and minimum SpO_2 were standardized using their respective sample SDs. One SD corresponded to 70.9 μmol/L for SUA, 10.7 mL/min/1.73 m² for eGFR, 0.13 mg/L for cystatin C, 9.7 events/h for ODI, and 2.8 percentage points for minimum SpO_2.

2.7 Data quality control and missing data

We retrospectively extracted assessments and examinations performed during hospitalization under standardized clinical workflows. Neurologists, sleep technologists, and research nurses involved in clinical assessments and data collection had received standardized training. PSG was performed by professional sleep technologists according to standard operating procedures, and MoCA, the Fried phenotype, Barthel Index, and PHQ-9 were administered by trained assessors using standardized instructions.

The research database was independently entered and cross-checked by two investigators. Apparent logical inconsistencies or outlying values were verified against the original medical records and examination reports. Patients with missing primary exposure data, primary outcomes, renal-function measures, or key PSG data were excluded during screening. Complete-case analysis was used for the primary analyses, and no imputation was performed for core variables.

2.8 Statistical analysis

Continuous variables are presented as mean (SD) or median [interquartile range], as appropriate, and categorical variables as number (percentage). For two-group comparisons, normally distributed continuous variables were compared using independent-samples t tests and non-normally distributed variables using Mann-Whitney U tests; categorical variables were compared using Pearson χ^2 or Fisher exact tests, as appropriate. Across SUA tertiles, continuous variables were compared using one-way analysis of variance or Kruskal-Wallis tests and categorical variables using χ^2 tests. *P* values for trend were obtained by entering the tertile category as an ordinal variable.

Multivariable linear regression was used for continuous outcomes and multivariable logistic regression for binary outcomes, including PSCI, moderate-to-severe SDB, and physical frailty. Results are reported as β coefficients or odds ratios (ORs), respectively, with 95% confidence intervals (CIs). Heteroscedasticity-robust standard errors were used in linear regression models. SUA was analyzed per 1-SD increase and by sex-specific tertiles.

For cognitive outcomes, four progressively adjusted models were specified. Model 1 included age and sex. Model 2 additionally included years of education, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, diuretic use, sedative-hypnotic use, and PHQ-9 score. Model 3 additionally included eGFR, and Model 4 additionally included ODI. Continuous SUA analyses report the β coefficient or OR per 1-SD increase with its 95% CI. Sex-specific SUA tertiles were analyzed using the fully adjusted Model 4, with T1 as the reference, and *P* values for trend were calculated. Changes in effect estimates across models were used to describe attenuation after additional adjustment for eGFR and ODI and were not interpreted as formal mediation.

Models examining SUA in relation to renal outcomes were adjusted for age, sex, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, and diuretic use. Models examining SUA in relation to sleep outcomes additionally adjusted for eGFR and sedative-hypnotic use. Analyses of renal markers in relation to sleep outcomes additionally adjusted for SUA; eGFR and cystatin C were entered in separate models.

Restricted cubic spline (RCS) models were used to examine dose-response patterns and potential nonlinearity in the associations of SUA with the education-adjusted MoCA score and PSCI. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the SUA distribution, with the median SUA as

the reference. RCS models were adjusted for the same covariates as Model 4, and overall and nonlinear associations were tested separately.

Associations of SUA, eGFR, ODI, and minimum SpO_2 with PSCI and physical frailty were evaluated in separate multivariable logistic regression models. Each model adjusted for age, sex, years of education, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, diuretic use, sedative-hypnotic use, and PHQ-9 score.

Because the number of physical frailty events was relatively limited in relation to the number of covariates in the fully adjusted models, two sensitivity analyses were performed. First, a prespecified parsimonious model adjusted for age, sex, years of education, BMI, diabetes, previous stroke, admission NIHSS score, prestroke mRS score, and PHQ-9 score. Second, Firth penalized-likelihood logistic regression was fitted while retaining all covariates from the fully adjusted model to reduce small-sample bias under limited event counts [21]. Each clinical marker was entered in a separate model.

All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

2.9 Ethics

The study was conducted in accordance with the Declaration of Helsinki [22] and was approved by the Ethics Committee of Yangzhou University (approval no. 2023-YKL09). Written informed consent had been obtained from all participants or their legally authorized representatives. All data used for analysis were anonymized or de-identified after extraction.

3.Results

3.1 Participant selection

Between January 2023 and January 2026, 682 patients with ischemic stroke were screened. We excluded 96 patients aged < 60 years, 31 with missing or technically inadequate PSG data, 24 with missing or incomplete MoCA assessments, 17 with missing SUA or renal-function data, 6 with a history of dementia or another severe neuropsychiatric disorder, and 8 who could not complete the required assessments because of severe aphasia, impaired consciousness, or other reasons. The final analytic sample comprised 500 participants: 270 without PSCI and 230 with PSCI, corresponding to a PSCI prevalence of 46.0% (Fig. 1).

3.2 Clinical characteristics according to PSCI status

The mean age of the included participants was 69.3 (5.5) years, and 235 (47.0%) were men. Compared with participants without PSCI, those with PSCI were older, had fewer years of education, had a slightly higher BMI, and had a higher admission NIHSS score (all $P < 0.05$). The groups did not differ significantly

in sex, smoking or drinking status, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, or prestroke mRS score (all $P > 0.05$).

SUA was higher in the PSCI group than in the non-PSCI group [407.6 (69.9) vs 364.9 (65.7) μmol/L]. Participants with PSCI also had higher SCr, BUN, cystatin C, and SUA/SCr ratios and lower eGFR [79.0 (10.6) vs 84.4 (10.2) mL/min/1.73 m²] (all $P < 0.01$).

Regarding sleep measures, participants with PSCI had higher AHI, ODI, T90, and arousal index and lower mean SpO_2, minimum SpO_2, sleep efficiency, N3 sleep percentage, and REM sleep percentage (all $P < 0.01$). They also had lower Barthel Index scores, higher Fried phenotype scores, and a higher prevalence of physical frailty. Physical frailty was present in 35.7% of participants with PSCI and 8.1% of those without PSCI ($P < 0.001$) (Table 1).

Table 1
Characteristics of patients according to post-stroke cognitive impairment status

Variable	Overall (N = 500)	Non-PSCI (n = 270)	PSCI (n = 230)	P value
Age, years	69.3 (5.5)	67.8 (5.1)	71.1 (5.5)	< 0.001
Male sex	235 (47.0%)	125 (46.3%)	110 (47.8%)	0.733
Education, years	9.9 (3.8)	10.6 (3.8)	9.0 (3.6)	< 0.001
BMI, kg/m²	24.6 (3.0)	24.3 (2.9)	24.9 (3.1)	0.033
Current smoking	104 (20.8%)	49 (18.1%)	55 (23.9%)	0.283
Current drinking	89 (17.8%)	45 (16.7%)	44 (19.1%)	0.343
Hypertension	335 (67.0%)	180 (66.7%)	155 (67.4%)	0.864
Diabetes mellitus	134 (26.8%)	75 (27.8%)	59 (25.7%)	0.593
Dyslipidemia	222 (44.4%)	115 (42.6%)	107 (46.5%)	0.378
Coronary heart disease	97 (19.4%)	46 (17.0%)	51 (22.2%)	0.148
Atrial fibrillation	47 (9.4%)	25 (9.3%)	22 (9.6%)	0.907
Previous stroke	117 (23.4%)	59 (21.9%)	58 (25.2%)	0.376
NIHSS at admission	5.0 [3.0–7.0]	4.0 [3.0–6.0]	6.0 [4.0–8.0]	< 0.001
Prestroke mRS	1.0 [0.0–1.0]	1.0 [0.0–1.0]	1.0 [0.0–1.0]	0.124
SUA, μmol/L	384.5 (70.9)	364.9 (65.7)	407.6 (69.9)	< 0.001
SCr, μmol/L	79.6 [72.7–88.0]	77.9 [70.6–85.5]	81.9 [74.9–89.8]	< 0.001
eGFR, mL/min/1.73 m²	81.9 (10.7)	84.4 (10.2)	79.0 (10.6)	< 0.001
BUN, mmol/L	5.50 (0.78)	5.41 (0.80)	5.61 (0.74)	0.003
Cystatin C, mg/L	0.96 (0.13)	0.93 (0.12)	0.98 (0.13)	< 0.001
SUA/SCr ratio	4.85 (0.84)	4.70 (0.81)	5.02 (0.85)	< 0.001
AHI, events/h	24.4 [17.2–30.8]	21.6 [14.5–28.6]	26.8 [20.6–33.1]	< 0.001

Notes: Data are presented as mean (SD), median [IQR], or n (%), as appropriate. P values were calculated using Student t tests, Mann-Whitney U tests, Pearson chi-square tests, or Fisher exact tests, as appropriate. PSCI was defined as an education-adjusted MoCA score < 26; one point was added for ≤ 12 years of education, without exceeding 30. Physical frailty was defined as an FP score ≥ 3. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FP, Fried phenotype; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; N3, stage N3 sleep; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; PSCI, post-stroke cognitive impairment; REM, rapid eye movement; SCr, serum creatinine; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T90, percentage of total sleep time with SpO_2 <90%.

Variable	Overall (N = 500)	Non-PSCI (n = 270)	PSCI (n = 230)	P value
ODI, events/h	17.9 [10.9–24.9]	14.8 [8.1–21.5]	22.2 [15.1–27.3]	< 0.001
T90, %	5.8 [3.9–9.1]	5.1 [3.6–8.1]	6.9 [4.4–10.5]	< 0.001
Mean SpO_2, %	94.5 (0.9)	94.7 (0.9)	94.3 (0.8)	< 0.001
Minimum SpO_2, %	84.8 (2.8)	85.4 (2.7)	84.1 (2.7)	< 0.001
Sleep efficiency, %	80.7 (5.3)	81.5 (5.2)	79.8 (5.3)	< 0.001
Arousal index, events/h	21.6 [16.4–26.0]	19.9 [15.0–24.4]	23.5 [19.0–27.5]	< 0.001
N3 sleep, %	11.9 (3.5)	12.6 (3.6)	11.1 (3.1)	< 0.001
REM sleep, %	17.0 (2.6)	17.3 (2.6)	16.6 (2.5)	0.005
Barthel Index	85.0 [76.0–93.0]	89.5 [81.2–95.0]	81.0 [72.0–87.0]	< 0.001
FP score	1.0 [1.0–2.0]	1.0 [0.0–2.0]	2.0 [1.0–3.0]	< 0.001
Physical frailty (FP ≥ 3)	104 (20.8%)	22 (8.1%)	82 (35.7%)	< 0.001

Notes: Data are presented as mean (SD), median [IQR], or n (%), as appropriate. P values were calculated using Student t tests, Mann-Whitney U tests, Pearson chi-square tests, or Fisher exact tests, as appropriate. PSCI was defined as an education-adjusted MoCA score < 26; one point was added for ≤ 12 years of education, without exceeding 30. Physical frailty was defined as an FP score ≥ 3. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FP, Fried phenotype; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; N3, stage N3 sleep; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; PSCI, post-stroke cognitive impairment; REM, rapid eye movement; SCr, serum creatinine; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T90, percentage of total sleep time with SpO_2 <90%.

3.3 Clinical characteristics across sex-specific SUA tertiles

Using sex-specific SUA tertiles, 166 participants were classified as T1, 166 as T2, and 168 as T3. Mean SUA levels were 309.9 (39.6), 384.5 (23.4), and 458.4 (43.4) μmol/L, respectively. Age, sex, years of education, BMI, admission NIHSS score, and total sleep time did not differ significantly across the three groups. The prevalence of diabetes increased from 15.7% in T1 to 35.1% in T3 (*P* for trend < 0.001).

Across increasing SUA tertiles, SCr, BUN, cystatin C, and the SUA/SCr ratio increased, whereas eGFR decreased (all *P* for trend < 0.001). AHI, ODI, T90, and arousal index increased, while mean SpO_2, minimum SpO_2, and N3 sleep percentage decreased (all *P* for trend ≤ 0.005). Sleep efficiency showed a modest downward trend (*P* for trend = 0.046), although the overall between-group comparison was not statistically significant (*P* = 0.136).

Cognitive and physical frailty outcomes showed parallel gradients. The education-adjusted MoCA score decreased from 26.4 (1.8) in T1 to 24.7 (1.6) in T3, the prevalence of PSCI increased from 31.9% to

64.9%, and the prevalence of physical frailty increased from 12.0% to 29.2% (all *P* for trend < 0.001). The Barthel Index also decreased across SUA tertiles (*P* for trend = 0.026) (Table 2).

Table 2
Characteristics across sex-specific serum uric acid tertiles

Variable	T1 (n = 166)	T2 (n = 166)	T3 (n = 168)	Overall P	P for trend
Age, years	69.4 (5.5)	69.5 (5.8)	69.0 (5.3)	0.720	0.533
Male sex	78 (47.0%)	78 (47.0%)	79 (47.0%)	1.000	0.995
Education, years	10.0 (4.0)	9.9 (3.8)	9.7 (3.5)	0.672	0.381
BMI, kg/m²	24.7 (2.9)	24.2 (3.2)	24.9 (2.9)	0.097	0.516
NIHSS at admission	5.0 [3.0–7.0]	5.0 [3.0–7.0]	5.0 [3.0–7.0]	0.843	0.622
Hypertension	105 (63.3%)	111 (66.9%)	119 (70.8%)	0.338	0.141
Diabetes mellitus	26 (15.7%)	49 (29.5%)	59 (35.1%)	< 0.001	< 0.001
SUA, μmol/L	309.9 (39.6)	384.5 (23.4)	458.4 (43.4)	< 0.001	< 0.001
SCr, μmol/L	75.8 [67.7–82.5]	80.1 [74.0–86.5]	83.5 [76.5–92.5]	< 0.001	< 0.001
eGFR, mL/min/1.73 m²	88.8 (9.9)	81.4 (8.9)	75.6 (9.0)	< 0.001	< 0.001
BUN, mmol/L	5.25 (0.78)	5.55 (0.72)	5.71 (0.77)	< 0.001	< 0.001
Cystatin C, mg/L	0.89 (0.12)	0.97 (0.12)	1.01 (0.12)	< 0.001	< 0.001
SUA/SCr ratio	4.18 (0.66)	4.86 (0.58)	5.50 (0.69)	< 0.001	< 0.001
AHI, events/h	19.7 [13.7–26.7]	24.4 [17.1–30.4]	27.8 [22.2–33.7]	< 0.001	< 0.001
ODI, events/h	11.2 [6.5–17.7]	19.5 [11.9–24.7]	24.3 [16.7–29.4]	< 0.001	< 0.001
T90, %	4.5 [2.9–6.5]	5.6 [3.9–8.3]	8.2 [5.5–11.4]	< 0.001	< 0.001
Mean SpO_2, %	94.9 (0.8)	94.5 (0.8)	94.2 (0.8)	< 0.001	< 0.001
Minimum SpO_2, %	85.8 (2.7)	84.8 (2.6)	83.7 (2.6)	< 0.001	< 0.001

Notes: Sex-specific SUA tertiles were generated separately in women and men. Cut points were 340.2 and 394.7 μmol/L in women and 374.2 and 431.9 μmol/L in men. Data are presented as mean (SD), median [IQR], or n (%), as appropriate. Overall P values were obtained using one-way analysis of variance, Kruskal-Wallis tests, Pearson chi-square tests, or Fisher exact tests, as appropriate. P for trend was calculated by entering the tertile category as an ordinal variable. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FP, Fried phenotype; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; N3, stage N3 sleep; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; PSCI, post-stroke cognitive impairment; REM, rapid eye movement; SCr, serum creatinine; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T1-T3, sex-specific SUA tertiles; T90, percentage of total sleep time with SpO_2 <90%.

Variable	T1 (n = 166)	T2 (n = 166)	T3 (n = 168)	Overall P	P for trend
Total sleep time, min	365.7 (34.7)	364.5 (36.7)	363.9 (31.0)	0.883	0.623
Sleep efficiency, %	81.3 (5.1)	80.7 (5.5)	80.1 (5.2)	0.136	0.046
Arousal index, events/h	18.6 [14.0–23.3]	21.5 [16.3–25.0]	24.5 [20.0–27.6]	< 0.001	< 0.001
N3 sleep, %	12.3 (3.5)	12.1 (3.3)	11.3 (3.4)	0.011	0.005
REM sleep, %	17.0 (2.6)	17.2 (2.8)	16.7 (2.4)	0.197	0.428
MoCA adjusted score	26.4 (1.8)	25.8 (1.9)	24.7 (1.6)	< 0.001	< 0.001
PSCI (MoCA < 26)	53 (31.9%)	68 (41.0%)	109 (64.9%)	< 0.001	< 0.001
Barthel Index	87.0 [78.0–94.0]	86.0 [75.2–93.8]	83.0 [75.0–92.0]	0.061	0.026
FP score	1.0 [0.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–3.0]	< 0.001	< 0.001
Physical frailty (FP ≥ 3)	20 (12.0%)	35 (21.1%)	49 (29.2%)	< 0.001	< 0.001

Notes: Sex-specific SUA tertiles were generated separately in women and men. Cut points were 340.2 and 394.7 μmol/L in women and 374.2 and 431.9 μmol/L in men. Data are presented as mean (SD), median [IQR], or n (%), as appropriate. Overall P values were obtained using one-way analysis of variance, Kruskal-Wallis tests, Pearson chi-square tests, or Fisher exact tests, as appropriate. P for trend was calculated by entering the tertile category as an ordinal variable. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FP, Fried phenotype; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; N3, stage N3 sleep; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; PSCI, post-stroke cognitive impairment; REM, rapid eye movement; SCr, serum creatinine; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T1-T3, sex-specific SUA tertiles; T90, percentage of total sleep time with SpO_2 <90%.

3.4 Multivariable associations of SUA with renal and sleep outcomes

After adjustment for demographic characteristics, lifestyle factors, vascular risk factors, stroke severity, and relevant medications, each 1-SD increase in SUA was associated with a 5.78 mL/min/1.73 m² lower eGFR (β=-5.78; 95% CI, -6.60 to -4.97; *P* < 0.001). A 1-SD higher SUA was also associated with higher SCr (β = 4.12 μmol/L; 95% CI, 3.33 to 4.92), higher BUN (β = 0.19 mmol/L; 95% CI, 0.12 to 0.26), and higher cystatin C (β = 0.045 mg/L; 95% CI, 0.034 to 0.057) (all *P* < 0.001).

After additional adjustment for eGFR and sedative-hypnotic use, each 1-SD increase in SUA was associated with higher AHI (β = 3.13 events/h; 95% CI, 2.09 to 4.16), ODI (β = 4.50 events/h; 95% CI, 3.69 to 5.31), and T90 (β = 2.00 percentage points; 95% CI, 1.43 to 2.57), as well as lower mean SpO_2 (β=-0.27 percentage points; 95% CI, -0.36 to -0.17) and minimum SpO_2 (β=-0.76 percentage points; 95% CI, -1.06

to -0.46) (all $P < 0.001$). Higher SUA was also associated with greater odds of moderate-to-severe SDB (OR = 1.50; 95% CI, 1.08 to 2.08; $P = 0.014$).

In analyses of renal markers and sleep outcomes, each 1-SD increase in eGFR was associated with lower AHI (β=-1.53; 95% CI, -2.62 to -0.44; $P = 0.006$) and ODI (β=-1.14; 95% CI, -1.96 to -0.31; $P = 0.007$). Each 1-SD increase in cystatin C was associated with higher AHI (β = 1.28; 95% CI, 0.26 to 2.29; $P = 0.014$) and ODI (β = 0.96; 95% CI, 0.15 to 1.77; $P = 0.019$). Fully adjusted associations of eGFR or cystatin C with T90, mean SpO_2, and minimum SpO_2 were not statistically significant (Table 3).

Table 3
Multivariable associations among serum uric acid, renal function, and sleep outcomes

Exposure	Outcome	Adjusted effect (95% CI)	P value
Panel A. SUA and renal outcomes			
SUA, per 1-SD increase	eGFR, mL/min/1.73 m²	β = -5.78 (-6.60 to -4.97)	< 0.001
SUA, per 1-SD increase	SCr, μmol/L	β = 4.12 (3.33 to 4.92)	< 0.001
SUA, per 1-SD increase	BUN, mmol/L	β = 0.19 (0.12 to 0.26)	< 0.001
SUA, per 1-SD increase	Cystatin C, mg/L	β = 0.045 (0.034 to 0.057)	< 0.001
Panel B. SUA and sleep outcomes			
SUA, per 1-SD increase	AHI, events/h	β = 3.13 (2.09 to 4.16)	< 0.001
SUA, per 1-SD increase	ODI, events/h	β = 4.50 (3.69 to 5.31)	< 0.001
SUA, per 1-SD increase	T90, %	β = 2.00 (1.43 to 2.57)	< 0.001
SUA, per 1-SD increase	Mean SpO_2, %	β = -0.27 (-0.36 to -0.17)	< 0.001
SUA, per 1-SD increase	Minimum SpO_2, %	β = -0.76 (-1.06 to -0.46)	< 0.001
SUA, per 1-SD increase	Moderate-to-severe SDB	OR = 1.50 (1.08 to 2.08)	0.014
Panel C. Renal markers and sleep outcomes			
eGFR, per 1-SD increase	AHI, events/h	β = -1.53 (-2.62 to -0.44)	0.006
eGFR, per 1-SD increase	ODI, events/h	β = -1.14 (-1.96 to -0.31)	0.007
eGFR, per 1-SD increase	T90, %	β = -0.22 (-0.74 to 0.30)	0.406
eGFR, per 1-SD increase	Mean SpO_2, %	β = 0.07 (-0.02 to 0.16)	0.142
eGFR, per 1-SD increase	Minimum SpO_2, %	β = 0.26 (-0.03 to 0.55)	0.074

Notes: SUA was standardized to the sample SD (70.9 μmol/L). eGFR and cystatin C were standardized to 10.7 mL/min/1.73 m² and 0.13 mg/L, respectively. Linear regression was used for continuous outcomes and logistic regression for moderate-to-severe SDB. Heteroscedasticity-robust standard errors were used in linear models. Panel A models were adjusted for age, sex, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, and diuretic use. Panel B models additionally included eGFR and sedative-hypnotic use. Panel C models included the Panel A covariates plus SUA and sedative-hypnotic use; eGFR and cystatin C were entered in separate models. Each outcome was modeled separately. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; OR, odds ratio; SCr, serum creatinine; SDB, sleep-disordered breathing; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T90, percentage of total sleep time with SpO_2 <90%.

Exposure	Outcome	Adjusted effect (95% CI)	P value
Panel A. SUA and renal outcomes			
Cystatin C, per 1-SD increase	AHI, events/h	β = 1.28 (0.26 to 2.29)	0.014
Cystatin C, per 1-SD increase	ODI, events/h	β = 0.96 (0.15 to 1.77)	0.019
Cystatin C, per 1-SD increase	T90, %	β = 0.09 (-0.33 to 0.51)	0.659
Cystatin C, per 1-SD increase	Mean SpO_2, %	β = -0.03 (-0.12 to 0.05)	0.436
Cystatin C, per 1-SD increase	Minimum SpO_2, %	β = -0.24 (-0.51 to 0.02)	0.072

Notes: SUA was standardized to the sample SD (70.9 μmol/L). eGFR and cystatin C were standardized to 10.7 mL/min/1.73 m² and 0.13 mg/L, respectively. Linear regression was used for continuous outcomes and logistic regression for moderate-to-severe SDB. Heteroscedasticity-robust standard errors were used in linear models. Panel A models were adjusted for age, sex, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, and diuretic use. Panel B models additionally included eGFR and sedative-hypnotic use. Panel C models included the Panel A covariates plus SUA and sedative-hypnotic use; eGFR and cystatin C were entered in separate models. Each outcome was modeled separately. Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; OR, odds ratio; SCr, serum creatinine; SDB, sleep-disordered breathing; SpO_2, peripheral oxygen saturation; SUA, serum uric acid; T90, percentage of total sleep time with SpO_2 <90%.

3.5 Progressive models for cognitive outcomes

In Model 1, adjusted for age and sex, each 1-SD increase in SUA was associated with a 0.79-point lower education-adjusted MoCA score (β=-0.79; 95% CI, -0.93 to -0.65; $P < 0.001$). The association was similar after further adjustment for education, BMI, smoking and drinking status, vascular risk factors, stroke severity, relevant medications, and PHQ-9 score (Model 2: β=-0.75; 95% CI, -0.89 to -0.61; $P < 0.001$). The estimate was attenuated after adding eGFR (Model 3: β=-0.60; 95% CI, -0.78 to -0.43) and further attenuated after adding ODI (Model 4: β=-0.43; 95% CI, -0.63 to -0.24), while remaining statistically significant (both $P < 0.001$).

For PSCI, the OR per 1-SD increase in SUA was 2.19 (95% CI, 1.75 to 2.75) in Model 1 and 2.46 (95% CI, 1.89 to 3.19) in Model 2. After additional adjustment for eGFR, the OR was 2.28 (95% CI, 1.68 to 3.08); after further adjustment for ODI, it decreased to 1.75 (95% CI, 1.26 to 2.43), while remaining statistically significant (both $P < 0.001$).

In the fully adjusted tertile analysis, T2 did not differ significantly from T1 in either MoCA score (β=-0.19; 95% CI, -0.55 to 0.17; $P = 0.311$) or odds of PSCI (OR = 1.01; 95% CI, 0.56 to 1.84; $P = 0.967$). Compared with T1, T3 was associated with a 0.86-point lower education-adjusted MoCA score (β=-0.86; 95% CI,

-1.25 to -0.46; *P* < 0.001) and higher odds of PSCI (OR = 2.41; 95% CI, 1.22 to 4.76; *P* = 0.011). Trend analyses showed a progressive decrease in MoCA score (β=-0.43 per tertile; 95% CI, -0.63 to -0.24; *P* < 0.001) and an increase in the odds of PSCI (OR = 1.59 per tertile; 95% CI, 1.14 to 2.24; *P* = 0.007) across increasing SUA tertiles (Table 4).

Table 4
Associations of serum uric acid with cognition in progressive models

Outcome	Model or comparison	Adjusted effect (95% CI)	P value
Panel A. SUA per 1-SD increase			
MoCA adjusted score	Model 1	β = -0.79 (-0.93 to -0.65)	< 0.001
MoCA adjusted score	Model 2	β = -0.75 (-0.89 to -0.61)	< 0.001
MoCA adjusted score	Model 3	β = -0.60 (-0.78 to -0.43)	< 0.001
MoCA adjusted score	Model 4	β = -0.43 (-0.63 to -0.24)	< 0.001
PSCI (MoCA < 26)	Model 1	OR = 2.19 (1.75 to 2.75)	< 0.001
PSCI (MoCA < 26)	Model 2	OR = 2.46 (1.89 to 3.19)	< 0.001
PSCI (MoCA < 26)	Model 3	OR = 2.28 (1.68 to 3.08)	< 0.001
PSCI (MoCA < 26)	Model 4	OR = 1.75 (1.26 to 2.43)	< 0.001
Panel B. Sex-specific SUA tertiles in Model 4			
MoCA adjusted score	T2 vs T1	β = -0.19 (-0.55 to 0.17)	0.311
MoCA adjusted score	T3 vs T1	β = -0.86 (-1.25 to -0.46)	< 0.001
MoCA adjusted score	P for trend	β = -0.43 (-0.63 to -0.24) per tertile	< 0.001
PSCI (MoCA < 26)	T2 vs T1	OR = 1.01 (0.56 to 1.84)	0.967
PSCI (MoCA < 26)	T3 vs T1	OR = 2.41 (1.22 to 4.76)	0.011
PSCI (MoCA < 26)	P for trend	OR = 1.59 (1.14 to 2.24) per tertile	0.007

Notes: SUA was standardized to the sample SD (70.9 μmol/L). Linear regression with heteroscedasticity-robust standard errors was used for the education-adjusted MoCA score, and logistic regression was used for PSCI. Model 1 was adjusted for age and sex. Model 2 additionally included education, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, diuretic use, sedative-hypnotic use, and PHQ-9 score. Model 3 additionally included eGFR. Model 4 additionally included ODI. Panel B used the fully adjusted Model 4 with T1 as the reference; P for trend was calculated by entering the tertile category as an ordinal variable. Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; OR, odds ratio; PHQ-9, 9-item Patient Health Questionnaire; PSCI, post-stroke cognitive impairment; SUA, serum uric acid; T1-T3, sex-specific SUA tertiles.

3.6 Restricted cubic spline analyses of SUA and cognitive outcomes

In fully adjusted RCS models, SUA showed significant overall associations with both the education-adjusted MoCA score and PSCI (both *P* for overall association < 0.001). As SUA increased, the adjusted MoCA score generally decreased, whereas the OR for PSCI generally increased. Tests for nonlinearity were not statistically significant (MoCA, *P* for nonlinearity = 0.073; PSCI, *P* for nonlinearity = 0.157), providing no evidence of a clear nonlinear relationship or threshold effect. Overall, the spline patterns were approximately linear and were consistent with the analyses of SUA per 1-SD increase. The 95% CIs widened toward the edges of the displayed SUA range, indicating greater uncertainty where observations were sparser (Fig. 2).

3.7 Associations of key clinical markers with PSCI and physical frailty

In separate fully adjusted logistic regression models, each 1-SD increase in SUA and ODI was associated with higher odds of PSCI, with ORs of 2.46 (95% CI, 1.89 to 3.19) and 2.57 (95% CI, 1.96 to 3.36), respectively. Each 1-SD increase in eGFR and minimum SpO_2 was associated with lower odds of PSCI, with ORs of 0.57 (95% CI, 0.45 to 0.72) and 0.59 (95% CI, 0.47 to 0.75), respectively (all *P* < 0.001).

For physical frailty, the adjusted ORs per 1-SD increase in SUA and ODI were 1.90 (95% CI, 1.45 to 2.50) and 2.06 (95% CI, 1.54 to 2.74), respectively. The corresponding ORs per 1-SD increase in eGFR and minimum SpO_2 were 0.64 (95% CI, 0.49 to 0.83) and 0.58 (95% CI, 0.44 to 0.76), respectively (all *P* < 0.001) (Fig. 3).

3.8 Sensitivity analyses for physical frailty

In the prespecified parsimonious models, each 1-SD increase in SUA and ODI remained associated with higher odds of physical frailty, with adjusted ORs of 1.92 (95% CI, 1.48 to 2.49) and 1.97 (95% CI, 1.50 to 2.57), respectively. Each 1-SD increase in eGFR and minimum SpO_2 remained associated with lower odds of physical frailty, with ORs of 0.64 (95% CI, 0.49 to 0.83) and 0.58 (95% CI, 0.45 to 0.76), respectively (all *P* < 0.001).

In Firth penalized logistic regression models retaining all covariates from the fully adjusted model, the directions and statistical significance of the associations of SUA, eGFR, ODI, and minimum SpO_2 with physical frailty were consistent with the primary analyses. These findings indicate that the associations with physical frailty were broadly robust to alternative covariate specifications and regression methods (Supplementary Table S1).

4.Discussion

4.1 Main findings

In this study of 500 older adults with ischemic stroke, we integrated SUA, multiple renal markers, standard overnight PSG, education-adjusted MoCA scores, and the Fried frailty phenotype to examine the relationships among urate metabolism, renal function, sleep-respiratory physiology, cognitive impairment, and physical frailty. Four findings were most notable. First, higher SUA was associated with lower eGFR and higher SCr, BUN, and cystatin C, as well as higher AHI, ODI, and T90 and lower mean and minimum SpO_2. Second, higher SUA was associated with poorer education-adjusted MoCA performance and higher odds of PSCI after comprehensive adjustment for demographic factors, vascular risk factors, stroke severity, relevant medications, and depressive symptoms. Third, the SUA-cognition effect estimates were attenuated after sequential inclusion of eGFR and ODI but remained statistically significant. Fourth, higher SUA and ODI and lower eGFR and minimum SpO_2 were associated with both PSCI and physical frailty, and the frailty findings were consistent in parsimonious and Firth penalized regression analyses.

The principal contribution of this study is therefore not simply to reproduce an association between SUA and PSCI. Rather, it places SUA within a broader physiological context by integrating renal function and objective sleep-respiratory measures in the same older stroke population, examining changes in the SUA effect estimates after sequential adjustment for eGFR and ODI, and extending the analysis to physical frailty as a major geriatric syndrome. The findings suggest that cognitive and physical vulnerability after stroke may cluster with several interrelated, but non-equivalent, physiological dimensions.

4.2 SUA, renal function, and post-stroke cognitive impairment

The relationship between SUA and cognitive function remains complex. As the end product of human purine metabolism, uric acid has antioxidant properties, yet persistently elevated SUA may also accompany oxidative stress, inflammation, endothelial dysfunction, and vascular injury [5]. Previous studies in populations with ischemic stroke or transient ischemic attack have associated higher SUA with poorer cognitive performance or greater odds of PSCI [6, 7, 23], broadly consistent with the direction observed in our study.

However, available evidence does not support a uniformly adverse interpretation of SUA. A recent systematic review and meta-analysis reported that, in some populations, higher SUA was associated with better global cognition, learning and memory, or executive function [24]. In the ARIC-NCS cohort, higher SUA was associated with better baseline cognitive performance but also with faster subsequent cognitive decline, while its association with incident dementia was substantially attenuated after adjustment for cardiovascular and metabolic factors [25]. Another long-term population-based cohort reported an association between higher SUA and increased dementia risk [26]. Differences across studies may reflect variation in age and sex distributions, vascular burden, renal function, SUA exposure ranges, cognitive assessment methods, follow-up duration, and covariate adjustment strategies.

Renal function is an important context for interpreting the relationship between SUA and cognition. Uric acid undergoes renal filtration, reabsorption, secretion, and excretion; thus, higher SUA may reflect increased production or metabolic burden, reduced renal clearance, or both. In our study, higher SUA was consistently associated with lower eGFR and higher SCr, BUN, and cystatin C. Previous studies have likewise suggested that eGFR may influence the association between SUA and post-stroke cognitive performance and that the SUA/SCr ratio may provide information partly distinct from SUA alone [6, 8, 9].

Observational evidence also links impaired renal function to cognitive impairment. Among patients with ischemic stroke, lower eGFR has been associated with poorer cognitive performance even after accounting for SUA, stroke severity, and other vascular risk factors [27]. A systematic review and meta-analysis reported a substantial burden of cognitive impairment in chronic kidney disease (CKD) [28], and recent clinical guidance has emphasized potential contributions from cerebrovascular injury, endothelial dysfunction, chronic inflammation, uremic factors, and shared vascular risk factors [29]. Higher cystatin C has also been associated with poorer cognitive performance and cognitive decline in older adults [30]. Considering eGFR, SCr, BUN, and cystatin C as complementary renal markers may therefore help place SUA within a more complete renal-metabolic context.

In the progressive models, the associations of SUA with MoCA and PSCI were attenuated after eGFR was added and attenuated further after ODI was included, although they remained statistically significant. This pattern suggests that renal function and intermittent hypoxemia may account for part of the shared variation between SUA and cognitive outcomes, but it does not establish mediation or a causal pathway. In the fully adjusted tertile analysis, only the highest SUA tertile was significantly associated with poorer MoCA performance and higher odds of PSCI, whereas the middle tertile did not differ significantly from the lowest tertile. RCS analyses further showed significant overall associations with both cognitive outcomes but no statistically significant evidence of nonlinearity (MoCA, *P* for nonlinearity = 0.073; PSCI, *P* for nonlinearity = 0.157). Thus, although adverse cognitive associations were most apparent at higher SUA levels in the categorical analysis, the data do not support a distinct threshold, inflection point, or statistically significant nonlinear relationship; overall, the dose-response pattern was approximately linear.

4.3 Intermittent hypoxemia and cognitive vulnerability

Another important finding was that higher SUA was associated with more severe sleep-respiratory events and nocturnal hypoxemia, while the SUA-cognition effect estimates were further attenuated after ODI was added to the cognitive models. SDB is common after stroke, and recurrent apnea and hypopnea can lead to intermittent hypoxia, sleep fragmentation, sympathetic activation, oxidative stress, systemic inflammation, and impaired cerebrovascular regulation [10, 11, 31]. These abnormalities may reduce cerebral resilience to ischemic injury and interfere with neural recovery and cognitive function.

AHI is the conventional measure of SDB severity but primarily quantifies the frequency of respiratory events per hour of sleep and does not fully characterize the depth, duration, or cumulative dose of

oxygen desaturation [32]. Patients with similar AHI values may therefore experience substantially different nocturnal hypoxemic burdens. Studies of hypoxic burden further illustrate that incorporating the depth and duration of respiratory event-related desaturation provides information beyond event frequency alone [33]. Importantly, the principal outcome in that hypoxic-burden study was cardiovascular mortality; we therefore cite it to support the concept of more comprehensive hypoxemia quantification rather than as direct evidence linking hypoxic burden to cognitive impairment.

With respect to cognition, a previous meta-analysis linked SDB to a higher risk of cognitive impairment and poorer executive function [11]. Longitudinal research in older adults further associated lower mean SpO_2 and higher T90 with cognitive decline over 5 years, while associations of AHI and ODI with cognitive change appeared to vary according to age, sex, and genetic background [34]. More recent work has also linked better sleep continuity and less sleep-disordered breathing with better global cognition [35]. These findings are directionally consistent with the higher AHI, ODI, and T90 and lower mean and minimum SpO_2 observed among participants with PSCI in our study.

In separate fully adjusted models, higher ODI and lower minimum SpO_2 were both associated with PSCI, suggesting that the frequency and severity of nocturnal hypoxemia may provide clinically relevant information beyond respiratory event counts alone. The additional attenuation of the SUA-cognition estimates after ODI adjustment indicates that intermittent hypoxemia may account for part of the shared variation, but this cannot be interpreted as formal mediation. Higher SUA, renal dysfunction, and nocturnal hypoxemia may share common determinants such as age, obesity, diabetes, vascular abnormalities, and other unmeasured factors, or may relate to cognition through partly independent and overlapping pathways.

Notably, eGFR and cystatin C were primarily associated with AHI and ODI, whereas their fully adjusted associations with T90, mean SpO_2, and minimum SpO_2 were not consistently significant. This finding suggests that renal function, respiratory event frequency, and hypoxemia severity are related but non-equivalent physiological dimensions and argues against simplifying these associations into a single continuous pathway in which every component is statistically significant.

Participants with PSCI also had lower sleep efficiency, lower N3 and REM sleep percentages, and a higher arousal index. Previous evidence suggests that sleep continuity, sleep architecture, and sleep-disordered breathing may provide partly distinct information relevant to cognitive function [35]. In the present study, however, sleep-architecture measures were mainly examined in descriptive group comparisons, were not core exposures, and were not subjected to comprehensive causal modeling. These findings should therefore be regarded as supportive rather than as evidence that altered sleep architecture mediates the association between SUA and PSCI.

4.4 Physical frailty and geriatric implications

Cognitive impairment and physical frailty frequently coexist after stroke and may jointly reflect loss of multisystem physiological reserve. In our cohort, physical frailty was substantially more prevalent among

participants with PSCI; higher SUA and ODI and lower eGFR and minimum SpO_2 were also associated with greater odds of physical frailty. Previous stroke cohorts have similarly linked physical and brain frailty to adverse cognitive and functional outcomes [13]. These observations reinforce the view that cognitive and physical vulnerability should not be considered in isolation in older adults with ischemic stroke.

A nationwide study of older adults reported associations between higher SUA and greater deficit-accumulation frailty and physical frailty [36]. That study used a multidimensional frailty index, whereas we used the Fried phenotype; the constructs are not identical, but both suggest that higher SUA may mark broader physiological vulnerability. Potential contributors to the association between SUA and frailty include chronic low-grade inflammation, oxidative stress, endothelial dysfunction, metabolic comorbidity, renal dysfunction, and impaired muscle function. Nutritional status, body composition, medication use, and overall disease burden may also influence both SUA and frailty. SUA is therefore more appropriately interpreted as a correlate of metabolic and physiological reserve than as a single causal determinant of physical frailty.

Population-based research in older adults has also linked frailty and prefrailty to poorer global cognitive performance [37]. The frailty definition used in that study differed from the five-component Fried phenotype applied here, and its participants were primarily community-dwelling older adults. It therefore supports the broader clustering of cognitive and physical vulnerability but cannot substitute directly for stroke-specific evidence.

We also found that higher ODI and lower minimum SpO_2 were associated with physical frailty. Intermittent hypoxia and sleep fragmentation may plausibly contribute to frailty through fatigue, sympathetic activation, inflammation, reduced muscle function, and lower daytime activity. Conversely, frailty may increase susceptibility to sleep-respiratory abnormalities through reduced activity, obesity, impaired respiratory muscle function, and a greater comorbidity burden. The relationship may therefore be bidirectional and complex.

Because 104 participants met criteria for physical frailty and the fully adjusted models contained multiple covariates, we performed prespecified parsimonious models and Firth penalized logistic regression as sensitivity analyses. Effect directions and magnitudes for SUA, eGFR, ODI, and minimum SpO_2 were broadly consistent across model specifications, reducing concern that the main findings were driven solely by overfitting or limited event counts. Nonetheless, sensitivity analyses cannot eliminate the limitations of cross-sectional data, residual confounding, or reverse association, and these findings require validation in independent prospective cohorts.

4.5 Clinical implications and future directions

The clinical relevance of these findings does not lie in using a single SUA measurement as an independent diagnostic tool for PSCI or physical frailty. Rather, the results highlight a potentially meaningful clustering of routinely available laboratory markers, renal function, sleep-respiratory

physiology, and geriatric vulnerability. SUA is inexpensive and readily available, but its interpretation should consider eGFR, SCr, cystatin C, urate-lowering medication, diuretic use, metabolic comorbidity, and nutritional status rather than treating SUA in isolation from renal function.

For older patients with stroke who have higher SUA together with lower eGFR, higher ODI, lower minimum SpO_2, or physical frailty, more comprehensive cognitive screening, renal assessment, recognition of SDB, and geriatric assessment may be reasonable. Such an approach would be intended to identify patients with greater multidimensional vulnerability who may merit further evaluation, rather than to assign deterministic risk on the basis of any single marker. Importantly, this study does not show that lowering SUA improves cognition or physical frailty and does not support urate-lowering treatment for the purpose of improving cognitive outcomes.

Future studies should use multicenter prospective longitudinal designs with repeated measurements of SUA, renal function, PSG variables, and cognition to establish temporal relationships among these abnormalities. Long-term cohort data suggest that variability in SUA is associated with white-matter volume, brain microstructural integrity, and cognitive change, indicating that dynamic exposure patterns may be more informative than a single measurement [38]. Future work should also incorporate stroke lesion location and volume, cerebral small-vessel disease burden, brain atrophy, inflammatory markers, nutritional status, body composition, and more comprehensive neuropsychological testing of executive function, memory, attention, and visuospatial ability.

In the sleep domain, future studies could quantify respiratory event-related hypoxic burden, area under the oxygen-desaturation curve, and other measures that capture the depth and duration of hypoxemia [33], and compare their incremental value with AHI, ODI, and minimum SpO_2. External validation, calibration analyses, and decision-curve analyses will also be needed to determine whether integrating SUA, renal function, hypoxemia, and physical frailty materially improves PSCI risk stratification beyond demonstrating statistical associations.

4.6 Strengths and limitations

This study has several strengths. First, in a relatively large sample of older adults with ischemic stroke, we integrated SUA, multiple renal markers, standard overnight PSG, cognitive function, activities of daily living, and the Fried frailty phenotype, allowing several clinically related dimensions to be examined within the same population. Second, SUA was analyzed as a continuous measure, per 1-SD increase, by sex-specific tertiles, and using RCS, reducing reliance on a single linear assumption or a uniform clinical cutoff. Third, the progressive cognitive models characterized changes in SUA effect estimates after sequential inclusion of eGFR and ODI. Fourth, associations with physical frailty were evaluated using both a parsimonious model and Firth penalized logistic regression, with broadly consistent results across model specifications.

Several limitations should also be acknowledged. First, the retrospective cross-sectional design precludes determination of the temporal sequence among higher SUA, renal dysfunction, intermittent

hypoxemia, cognitive impairment, and physical frailty; causal inference and formal mediation analyses are therefore not possible. Second, this was a single-center study of hospitalized neurology patients, and patients with severe aphasia, impaired consciousness, or inability to complete MoCA or PSG assessments were excluded. Selection bias is therefore possible, and the findings are most applicable to older adults with ischemic stroke who can complete these assessments; generalization to patients with severe stroke, community populations, or other healthcare settings should be cautious.

Third, although the models adjusted for multiple demographic characteristics, vascular risk factors, stroke severity, medications, and depressive symptoms, residual confounding remains possible. Stroke lesion location and volume, cerebral small-vessel disease burden, prestroke cognitive status, history of gout, dietary purine intake, duration of chronic kidney disease, inflammatory status, nutritional status, and medication dose were not comprehensively assessed. Fourth, SUA, renal-function measures, and PSG variables were primarily based on single in-hospital measurements and may have been influenced by acute stroke-related responses, the hospital environment, and first-night effects; they therefore may not reflect long-term exposure or within-person variability.

Fifth, MoCA is a screening instrument rather than a comprehensive neuropsychological battery and cannot fully characterize impairment across specific cognitive domains. A uniform cutoff for PSCI may remain sensitive to educational, cultural, language, and stroke-related functional factors despite the education correction. Sixth, walking speed and grip strength within the Fried phenotype may be affected by post-stroke hemiparesis and motor disability and may therefore partly reflect current stroke severity rather than purely systemic or prestroke frailty.

Seventh, we did not calculate more refined hypoxemia metrics such as respiratory event-related hypoxic burden, and longitudinal cognitive follow-up, quantitative neuroimaging, and independent external validation were unavailable. Finally, multiple interrelated exposures and outcomes were examined. Although the analytic framework was based on prespecified clinical hypotheses, some exploratory findings may remain susceptible to multiple-comparison effects and require replication in independent cohorts.

5. Conclusions

In older adults with ischemic stroke, higher SUA was associated with poorer renal function, more severe sleep-respiratory abnormalities and intermittent hypoxemia, poorer cognitive performance, and physical frailty. The associations of SUA with the education-adjusted MoCA score and PSCI persisted after adjustment for demographic characteristics, vascular risk factors, stroke severity, relevant medications, and depressive symptoms; the estimates were attenuated but not eliminated after further adjustment for eGFR and ODI, suggesting that renal function and intermittent hypoxemia may account for part of the shared variation.

SUA, eGFR, ODI, and minimum SpO_2 also showed directionally consistent associations with both PSCI and physical frailty, supporting the concept that metabolic status, renal function, nocturnal hypoxemia,

and physical vulnerability may cluster within a complex clinical phenotype in older stroke populations. Simultaneous attention to cognition, renal function, sleep-respiratory physiology, and frailty may be useful in clinical assessment and future risk research, but the incremental predictive value and clinical utility of this integrated approach require validation in multicenter prospective studies.

Abbreviations

AASM, American Academy of Sleep Medicine

AHI, apnea-hypopnea index

BMI, body mass index

BUN, blood urea nitrogen

CI, confidence interval

CKD, chronic kidney disease

eGFR, estimated glomerular filtration rate

FP, Fried phenotype

IQR, interquartile range

MoCA, Montreal Cognitive Assessment

mRS, modified Rankin Scale

NIHSS, National Institutes of Health Stroke Scale

ODI, oxygen desaturation index

OR, odds ratio

PHQ-9, 9-item Patient Health Questionnaire

PSCI, post-stroke cognitive impairment

PSG, polysomnography

RCS, restricted cubic spline

REM, rapid eye movement

SCr, serum creatinine

SD, standard deviation

SDB, sleep-disordered breathing

SpO_2, peripheral oxygen saturation

SUA, serum uric acid

T90, percentage of total sleep time with SpO_2 <90%

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Yangzhou University (approval no. 2023-YKL09) and was conducted in accordance with the Declaration of Helsinki. Written informed consent had been obtained from all participants or their legally authorized representatives, and all data used for analysis were anonymized or de-identified.

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain sensitive patient information and are subject to institutional privacy and ethical restrictions. De-identified data may be available from the corresponding author, Cheng Chu, upon reasonable request and subject to approval by the relevant institutional and ethics authorities.

Competing interests

The authors declare that they have no competing interests.

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design, data collection, data analysis or interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Authors' contributions

YL contributed to the methodology, investigation, data curation, formal analysis, visualization, and drafting of the original manuscript, and participated in reviewing and editing the manuscript. YY, ZJ, and TJ contributed to the investigation, data curation, validation, and review and editing of the manuscript. NL contributed to the methodology, supervision, and critical review and editing of the manuscript. CC contributed to the conceptualization, methodology, supervision, project administration, funding acquisition, and critical review and editing of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Figures

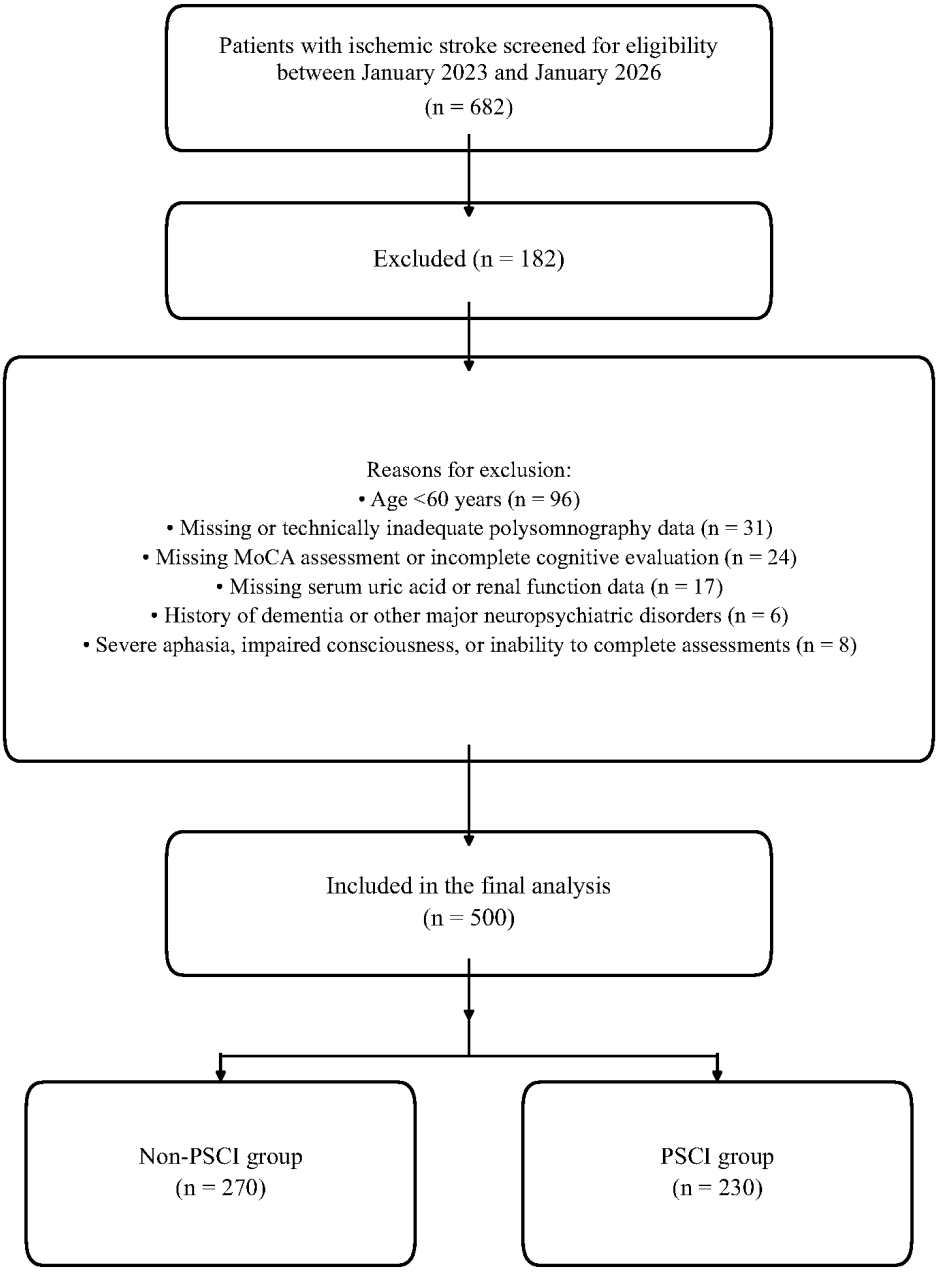


Figure 1

Flow diagram of participant selection. Of 682 patients with ischemic stroke screened between January 2023 and January 2026, 500 were included in the final analysis, comprising 270 participants without PSCI and 230 with PSCI.

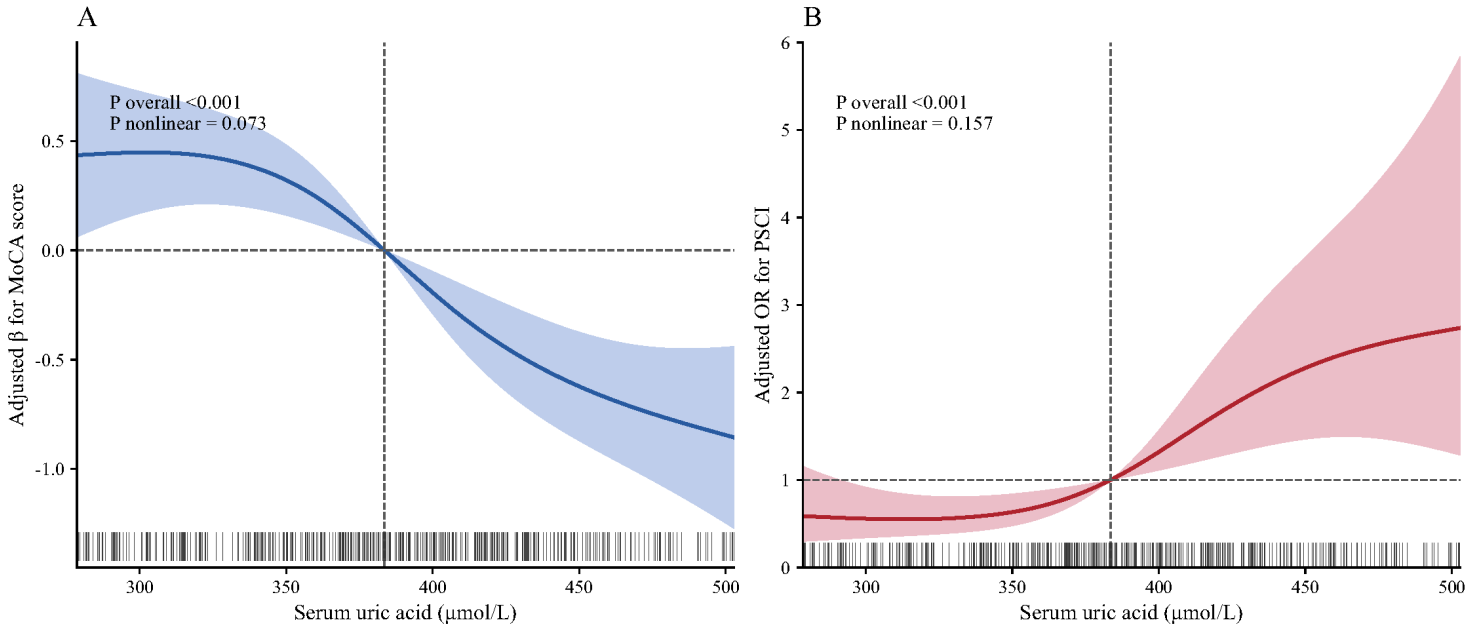


Figure 2

Restricted cubic spline associations of serum uric acid with cognitive outcomes. Panel A shows the association of SUA with the education-adjusted MoCA score, expressed as the adjusted β relative to the median SUA level. Panel B shows the association of SUA with PSCI, expressed as the adjusted OR relative to the median SUA level. Models used four knots at the 5th, 35th, 65th, and 95th percentiles of SUA and were adjusted for the covariates in Model 4. Solid lines indicate adjusted estimates, shaded areas indicate 95% CIs, and rug marks indicate the distribution of SUA. The vertical dashed line represents the median SUA; horizontal dashed lines represent β=0 in panel A and OR=1 in panel B. Overall associations were significant for both outcomes (both *P*<0.001), whereas tests for nonlinearity were not significant (MoCA, *P*=0.073; PSCI, *P*=0.157).

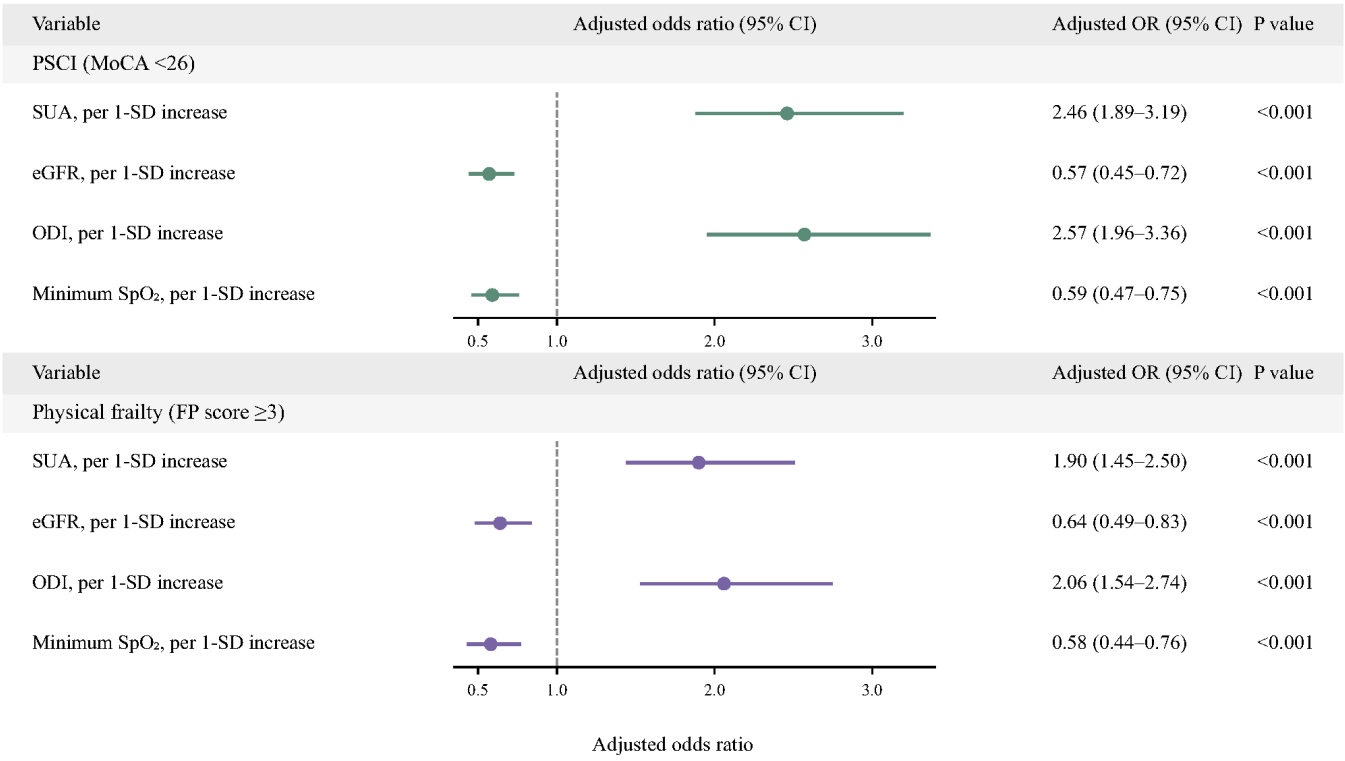


Figure 3

Adjusted associations of key clinical markers with PSCI and physical frailty. SUA, eGFR, ODI, and minimum SpO_2 were evaluated separately in multivariable logistic regression models and analyzed per 1-SD increase (70.9 μmol/L, 10.7 mL/min/1.73 m², 9.7 events/h, and 2.8 percentage points, respectively). Models were adjusted for age, sex, education, BMI, current smoking, current drinking, hypertension, diabetes, dyslipidemia, coronary heart disease, atrial fibrillation, previous stroke, admission NIHSS score, prestroke mRS score, urate-lowering medication, diuretic use, sedative-hypnotic use, and PHQ-9 score. Points indicate adjusted ORs and horizontal lines indicate 95% CIs.

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