Association of serum uric acid with risk of stroke in US adults: A cross-sectional study from NHANES 1999−2020

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Background and aims: The validity of high uric acid levels as an independent cause of stroke remains controversial, and the association between its low concentration and stroke is unclear. This study determines how different serum uric acid (SUA) levels are associated with stroke risk. *Methods:* This cross-sectional study used continuous National Health and Nutrition Examination Survey data in the United States during 1999−2020. The SUA levels of 6.0, 6.8, and 9.0 mg/dL were all considered as cut-off points. Restricted cubic spline interpolation and logistic regression models were used to evaluate the different associations. Subgroup analyses and sensitivity analyses were conducted to evaluate the influence of multiple factors on the outcomes. *Results:* The study included 23,413 participants aged ≥ 20 years. A J-shaped curve existed between SUA and stroke risk, and the risk of stroke was positively correlated with SUA levels in the overall population. Subgroup analysis of all adults in the SUA 6.8−9.0 mg/dL group showed that stroke risk for non-Hispanic white, obese, ex-smoker, and heavy drinking groups was increased, but for the other Hispanic group was reduced. In the SUA < 6.0 mg/dL group, stroke risk for ex-smoker, heavy drinkers, and no chronic kidney disease groups was increased. *Conclusion:* Our findings indicate a J-shaped relationship between SUA levels and stroke risk. Low and high SUA levels increased stroke risk for different populations, except in the other Hispanic population. Early SUA management is highly significant for stroke prevention in high-risk populations.

Keywords: Uric acid—Stroke—Hyperuricemia—Hypouricemia—NHANES

Introduction

Stroke is the second-most global death cause, only after ischemic heart disease, and third-most contributor to disability[1], making it a major therapeutic challenge. More than 100 million individuals worldwide experience stroke every year, of which 795,000 cases are in the United States.[2] Therefore, improved preventive strategies are needed; particularly, strategies targeting the modifiable risk factors of stroke, such as hypertension, hyperglycemia, and dyslipidemia, may help prevent more than approximately 90% of stroke cases.[3, 4] Recognition of the

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Glu, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SUA, Serum Uric Acid; TC, total cholesterol; TG, triglyceride; UA, uric acid; ULT, urate-lowering therapy

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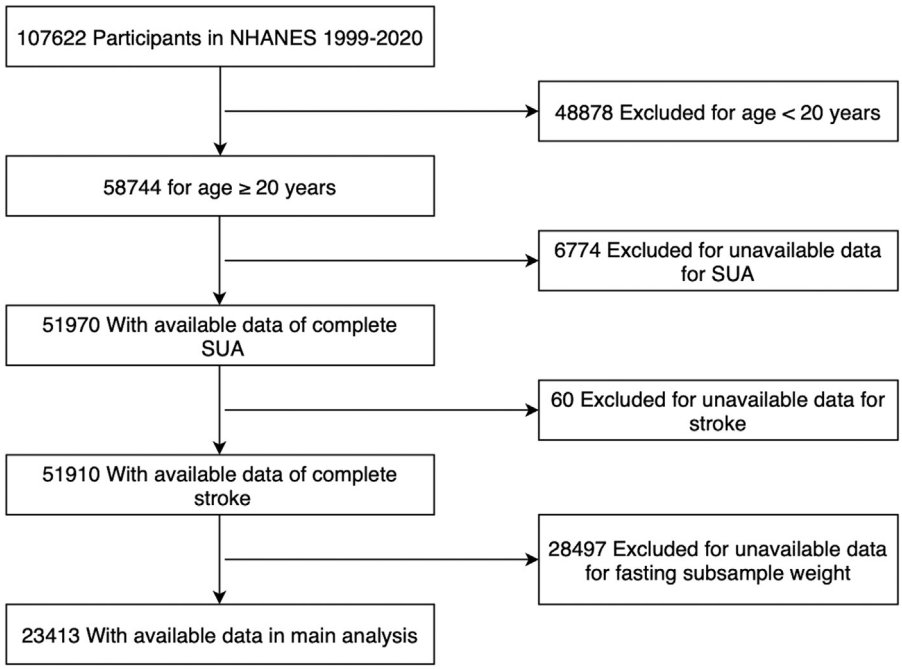

Fig. 1. *A flowchart showing the selection of study participants.*
Abbreviation: NHANES, National Health and Nutrition Examination Survey; SUA, Serum Uric Acid.

potential risk factors for stroke can help to develop effective preventive and therapeutic strategies.

Uric acid (UA) is considered a strong risk factor for stroke.[5] Produced as a byproduct of purine metabolism, UA is then converted into ammonia and ultimately excreted mainly via the kidney.[6] Serum uric acid (SUA) levels can increase due to a high-purine diet or additional dietary factors (e.g., alcohol and fructose consumption) that degrade purine nucleotides.[7] Because of the limited concentrations of uricase enzyme, which converts UA into its more soluble and excretable form, the theoretical limit of UA solubility in human serum is 6.8 mg/dL.[8, 9] Hyperuricemia refers to an abnormally high SUA levels (≥ 6.8 mg/dL)[8] without gout symptoms, and mainly occurs due to aberrant purine metabolism. Additionally, hyperuricemia is closely correlated with a higher risk of cardiovascular disease, kidney disease and metabolic syndrome.[10] UA plays an important antioxidant role in the pathophysiology of obesity, type 2 diabetes, hypertension, chronic renal disease, and coronary artery disease.[10-12] Hyperuricemia is an independent risk factor for stroke.[13,14] However, whether UA is a modifiable risk marker for stroke remains controversial.

The US Guideline for the Management of Gout recommends maintaining UA levels below 6 mg/dL; however, it has been indicated that low UA levels may have a detrimental effect on mortality in stroke.[15] The correlation between low UA levels (< 6.0 mg/dL) and stroke risk requires further elucidation. Furthermore, asymptomatic hyperuricemia patients may have a significantly increased stroke risk.[16] The US Guidelines for the Management of Gout conditionally oppose the use of urate-lowering therapy (ULT) in asymptomatic hyperuricemia patients[9]. However, ULT could help ensure a lower risk of stroke and death in patients with gout.[17] Which patient groups have a greater stroke risk due to UA levels remain unclear. Hence, it is difficult for clinicians to determine the need for ULT among asymptomatic hyperuricemia patients while considering additional costs and potential adverse drug reactions versus the lack of supporting evidence for stroke prevention.

Therefore, this study investigates the relationship between different SUA levels and stroke risk using a representative national cohort from the National Health and Nutrition Examination Survey (NHANES). We also explore population differences in SUA levels based on age, sex, race, and other factors to outline a high-risk population for stroke and provide a reference for clinical decision-making.

Materials and methods

Study population

The data analyzed in this study were retrieved from all NHANES cycles (1999−2020); the total sample size comprised 107,622. Individuals younger than 20 years of age with unavailable SUA or stroke data were excluded (n = 55,712). In addition, records containing missing values or values of 0 for the fasting subsample weights were not included (n = 28,497). Ultimately, 23,413 individuals were included (Fig. 1).

Informed consent was provided by all participants prior to doing the survey. A review board for the National Center for Health Statistics of the Centers for Disease Control ethics committee approved the protocol for the NHANES research. The present study did not require informed consent as the publicly available data were analyzed in a secondary form. The STROBE guidelines (checklist S1 of STROBE) were followed when preparing the current report.[18]

Primary Exposure

In the NHANES 1999−2020, participants aged ≥ 12 years met the requirements for the SUA examination. The methodological details of SUA detection are described in the Laboratory Procedure Manual officially provided by the NHANES. All laboratory variables were evaluated using validated protocols and procedures. Further information can be obtained on the NHANES official website (https://www.cdc.gov/nchs/nhanes). A total of 67,530 eligible participants completed this test, whereas 5,610 failed to do so. The SUA levels were categorized into clinically relevant categories of < 6.0 (Group 1), 6.0−6.7 (Group 2), 6.8−9.0 (Group 3), and > 9.0 mg/dL (Group 4). Multiply by 59.48 to convert SUA from mg/dL to μmol/L.

Outcomes

We used self-reported medical history of stroke. Stroke history was obtained through structured questionnaires delivered by trained interviewers in a home setting.

Covariates

Potential confounders related to the outcomes were considered covariates based on previously described methods and clinical practice. Demographics, such as age, sex, race, and stroke risk factors, were obtained from questionnaires, physical examinations, and laboratory testing during the baseline assessment visit. Age was classified into seven categories. Patients aged < 80 years were categorized into groups for each decade, and those aged ≥ 80 years represented one group. Race was categorized as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other ethnic groups. Educational attainment was categorized as high school or less, college, and college graduate. According to the latest NHANES classification, marital status was classified as married/living with a partner, widowed/divorced/separated, and never married. We used the poverty-to-income ratio, which compares a family's income to the poverty line, to evaluate income levels and establish eligibility for federal aid programs. These ratios were categorized as < 130%, 130%−180%, >180%.[19] The body mass index (BMI) classified body weight status into three groups: < 25.0 kg/m^2, 25.0−29.9 kg/m^2, and ≥ 30 kg/m^2. Physical activity was categorized into sedentary and non-sedentary behaviors. Participants who responded "No" to performing any of the activities in the questionnaire were considered to have sedentary behavior, which included walking or bicycling, task around the home or yard, muscle strengthening activities, work activity, and recreational activity.[20] Otherwise, they were considered to not have sedentary behavior. Smokers were categorized as never, former, and current smokers. Based on alcohol intake, participants were categorized as non-drinkers, moderate drinkers (1−2 drinks per day for men or 1 drink a day for women), and heavy drinkers (> 2 drinks a day for men or > 1 drink a day for women).[21]

Blood pressure values were calculated as averaged over multiple measurements taken at the same visit in the mobile examination center. Medical definitions were: Hypertension, systolic blood pressure exceeding 140 mmHg, diastolic blood pressure exceeding 90 mmHg, ongoing treatment with antihypertensive medications, and history of hypertension; Diabetes, glycated hemoglobin A1c (HbA1c) values of 6.5%, fasting blood glucose (Glu) levels > 7.0 mmol/L, current use of antidiabetic drugs, or present diabetes history[22]; Hyperlipidemia, total cholesterol (TC) levels ≥ 200 mg/dL, triglyceride (TG) levels ≥ 150 mg/dL, low-density lipoprotein cholesterol (LDL-C) levels ≥ 130 mg/dL, high-density lipoprotein cholesterol (HDL-C) levels < 40 mg/dL (for men), HDL-C levels < 50 mg/dL (for women), or treatment with lipid-lowering agents[23]; Chronic kidney disease (CKD), an albumin-to-creatinine ratio greater than 30 mg/L or an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2.[24] The eGFR was measured using the Modification of Diet in Renal Disease.[25] History of coronary heart disease (CHD), cancer, and medication use (including antihypertensive, antihyperlipidemic, antidiabetic, antiplatelet, anticoagulant, antigout, corticosteroids, and diuretics) were obtained from the standardized questionnaire. Serum albumin, serum creatinine, urinary albumin, urinary creatinine, blood urea nitrogen, Glu, HbA1c, TC, TG, LDL-C, HDL-C, total bilirubin, alanine aminotransferase, aspartate aminotransferase, white blood cell count, neutrophil cell count, lymphocyte cell count, platelet count, hemoglobin, and red blood cell distribution width were acquired through inspection of laboratory results.

Statistical Analysis

The weighted mean ± standard error was used for continuous variables. For between-group comparisons, we used an independent samples t-test or a one-way ANOVA. Categorical variables are given as weighted percentages with a 95% confidence interval (95% CI). A chi-square test was used for group comparisons. Restricted cubic splines of continuous SUA were applied to graphically evaluate the potential nonlinear association between SUA levels and stroke after adjusting for sex, age, race,

body mass index (BMI), physical activity, smoking, alcohol intake, coronary heart disease (CHD), hypertension, diabetes, hyperlipidemia, chronic kidney disease (CKD), red blood cell distribution width, and antiplatelet, anticoagulant, and antigout medication. Based on logistic regression models, with SUA 6.0−6.7 mg/dL as the reference, the odds ratio (OR) was calculated to estimate the risk of stroke associated with SUA classification levels. Age, sex, and race were adjusted in the micro-adjustment model, and all aforementioned variables were adjusted in the full adjustment model. Linear trend tests were performed for the UA categorize variables.

Given the effect of antigout drugs on SUA levels, we adjusted for antigout medication use in the major analysis. After excluding antigout medication users, we conducted a sensitivity analysis using logistic regression.

Furthermore, subgroup analyses were conducted to assess the effect of sex, age, race, BMI, smoking, drinking, hypertension, CKD, and diuretics on stroke outcomes. The potential interactions between each stratified variable and SUA levels were explored using an interaction test in the final model.

All data analyses and graphs were performed using R 4.2.0 (https://www.r-project.org) and Empower Stats 4.1 epidemiology program (www.empowerstats.com). The NHANES's complicated survey design was simplified by using representative weights from the fasting subsamples. Details can be obtained from the official website: https://www.cdc.gov/nchs/nhanes/tutorials/module3.aspx. In all analyses, a two-sided P-value < 0.05 denoted statistical significance.

Results

Characteristics of participants

A total of 23,413 individuals were included in the study, representing 215.9 million noninstitutionalized residents of the United States in 1999−2020. Table 1 displays the baseline characteristics of study participants by SUA grouping. The overall prevalence of stroke was 3.1%, and stroke risk increased with increasing SUA levels and was up to 10.4% in Group 4. A statistically significant correlation was obtained for almost all outcomes across the SUA grouping, except for cancer and corticosteroid use ($P > 0.05$).

Compared to those with lower SUA levels, participants with higher levels of SUA tended to be older (predominantly 60−69 years old), male, non-Hispanic white, obese (BMI $\geq$ 30 kg/m^2), non-smokers, and heavy drinkers. Individuals with higher SUA levels were more likely to take medication and have diabetes, hyperlipidemia, hypertension, CKD, or CHD. Conversely, the estimated glomerular filtration rate and high-density lipoprotein cholesterol levels were negatively associated with SUA levels across grouping. No significant trend was observed for physical activity.

Associations Between SUA Levels and Stroke Risk

Restricted cubic spline analyses revealed a J-shaped curve between UA and stroke risk in all participants (Fig. 2).

The associations between SUA levels and stroke risk in overall participants are presented in Table 2. SUA concentrations and stroke risk were significantly correlated in each model in Group 4. Moreover, the trend test results for all groups were statistically significant ($P < 0.001$). In the full adjustment models, individuals in Group 4 had a 66.0% higher risk of stroke ($P = 0.049$). The relationship between SUA levels and stroke risk might be affected by antigout medication use, despite only 2% of the individuals taking it. As SUA levels increase, the proportion of antigout medication users becomes larger (Table 1). A sensitivity analysis was conducted to avoid this impact. Notably, in all models, the results remained essentially unchanged for participants who did not use antigout medications. Sensitivity analyses yielded largely consistent results. In Group 4, under the full adjustment models, after sensitivity analysis, individuals had an 70.0% higher risk of stroke ($P = 0.0498$).

Fig. 3 presents the subgroup analysis results for the overall population under the full adjustment model. The results showed that part of the participants with low and high SUA levels had a significantly increased of stroke risk. Participants aged $\geq$ 80 years in Group 4 had a 2.45-fold increase in the risk for stroke ($P = 0.005$). Non-Hispanic whites in Group 3 had an OR = 1.49 [95% CI, 1.02−2.18, $P = 0.040$] and in Group 4 an OR = 2.13 [95% CI, 1.11−4.09, $P = 0.024$] was observed. Participants with BMI $\geq$ 30 kg/m^2 in Group 3 showed an OR = 1.81 for stroke risk [95% CI, 1.17−2.80, $P = 0.009$]. Former smokers in Group 1 and Group 3 had 80% ($P = 0.016$) and 99% ($P = 0.012$) higher risk of stroke, respectively. The heavy drinkers in Group 1 had an OR = 1.89 [95% CI, 1.25−2.87, $P = 0.003$], and those in Group 3 had an OR = 1.74 [95% CI, 1.08−2.82, $P = 0.023$]. Individuals without CKD in Group 1 had a 1.52-fold risk of stroke ($P = 0.017$). Participants in Group 4 that used diuretics had up to 113% increased risk of stroke ($P = 0.016$). Inversely, other Hispanic individuals in Group 3 showed a significantly decreased stroke risk by 93% ($P = 0.008$). Subgroup analyses revealed no statistical differences related to sex or hypertension. Trend test results in each subgroup analysis were statistically significant ($P < 0.001$).

There was a significant interaction between smoking status and CKD and SUA levels under the full adjustment model ($P = 0.030$ and $P = 0.013$, respectively). No significant interaction was observed in any other predefined subgroups.

Since there were no participants aged 20−29 years in Group 3, 20−49 years in Group 4 (Fig. 3), we conducted further analysis on participants aged $\geq$ 50 years (Supplemental Results, Supplemental Tables 1-4, and Supplemental Fig.1).

Table 1. *Weighted characteristics of the overall participants based on SUA grouping*

Characters	Total (n=23413)	Group 1 (< 6.0) (n=15435)	Group 2 (6.0-6.7) (n=3828)	Group 3 (6.8-9.0) (n=3801)	Group 4 (>9.0) (n=349)	P-value
Age (years)	47.0±0.2	46.1±0.3	47.7±0.4	49.3±0.4	54.9±1.3	<0.001
20-29	18.7 (17.6-19.9)	19.6 (18.5-20.8)	18.0 (16.2-19.8)	16.5 (14.9-18.2)	9.6 (5.1-14.1)	
30-39	18.9 (17.9-19.8)	19.7 (18.7-20.6)	18.7 (17.1-20.4)	16.0 (14.2-17.7)	15.4 (8.2-22.6)	
40-49	19.6 (18.5-20.7)	20.0 (19.1-21.0)	19.0 (17.3-20.8)	18.5 (16.7-20.2)	15.1 (8.8-21.4)	
50-59	17.7 (16.7-18.8)	17.7 (16.8-18.6)	17.0 (15.5-18.6)	18.5 (16.9-20.1)	16.2 (10.9-21.5)	
60-69	13.4 (12.5-14.4)	12.4 (11.5-13.2)	15.2 (13.8-16.6)	15.5 (14.1-17.0)	20.6 (14.3-26.9)	
70-79	7.8 (7.3-8.3)	7.2 (6.7-7.6)	7.8 (6.8-8.7)	9.9 (8.8-11.0)	11.9 (8.2-15.6)	
≥80	4.0 (3.6-4.3)	3.5 (3.1-3.8)	4.3 (3.7-5.0)	5.1 (4.5-5.7)	11.2 (7.9-14.5)	
Male (%)	48.3 (46.4-50.3)	35.3 (34.4-36.3)	69.1 (67.1-71.0)	78.2 (76.7-79.7)	73.3 (67.0-79.7)	<0.001
Race (%)						<0.001
Mexican American	8.3 (7.3-9.2)	8.9 (7.8-10.0)	8.0 (6.7-9.4)	6.2 (5.1-7.3)	4.6 (2.8-6.4)	
Other Hispanic	5.7 (4.8-6.6)	6.2 (5.2-7.2)	5.1 (4.1-6.1)	4.6 (3.6-5.7)	4.9 (2.7-7.0)	
Non-Hispanic White 67.9 (63.8-71.9)66.8 (64.8-68.8) 69.4 (66.8-72.0)70.8 (68.2-73.4)66.6 (60.2-73.0)	67.9 (63.8-71.9)	66.8 (64.8-68.8)	69.4 (66.8-72.0)	70.8 (68.2-73.4)	66.6 (60.2-73.0)	
Non-Hispanic Black	11.1 (10.1-12.1)	11.0 (9.8-12.1)	10.5 (9.2-11.9)	11.4 (9.9-12.9)	17.3 (13.2-21.4)	
Other races[a]	7.1 (6.4-7.8)	7.2 (6.5-7.9)	6.9 (5.9-7.9)	7.0 (5.8-8.2)	6.7 (3.3-10.1)	
Education (%)						0.010
High school or less	41.0 (38.9-43.1)	40.4 (38.7-42.0)	42.4 (40.2-44.6)	41.4 (39.1-43.8)	51.7 (44.6-58.9)	
Some college	30.8 (29.3-32.3)	30.5 (29.3-31.7)	31.0 (29.2-32.7)	31.6 (29.5-33.8)	31.1 (23.5-38.7)	
College graduate	28.1 (26.3-30.0)	29.1 (27.4-30.7)	26.6 (24.4-28.8)	26.8 (24.7-28.9)	17.1 (11.3-22.8)	
Marital status (%)						0.020
Married/Living with Partner	63.9 (61.0-66.7)	63.5 (62.1-64.9)	65.4 (63.3-67.5)	64.3 (62.0-66.7)	58.0 (49.8-66.3)	
Widowed/Divorced/Separated	17.8 (16.7-18.8)	18.4 (17.4-19.4)	15.4 (13.9-16.9)	17.3 (15.7-18.8)	25.0 (18.7-31.3)	
Never married	17.4 (16.3-18.5)	17.1 (16.0-18.2)	18.3 (16.3-20.3)	17.7 (16.0-19.5)	15.7 (10.9-20.5)	
Poverty-income ratio (%)						0.010
<130%	19.3 (18.1-20.5)	20.1 (18.8-21.3)	18.9 (17.2-20.6)	16.6 (15.1-18.0)	20.6 (15.8-25.4)	
130% −180%	9.3 (8.6-10.0)	9.1 (8.5-9.7)	9.4 (8.3-10.5)	10.0 (8.8-11.2)	12.6 (9.2-16.0)	
>180%	64.3 (61.3-67.4)	63.8 (62.2-65.3)	64.7 (62.4-66.9)	66.8 (64.7-68.9)	59.6 (52.8-66.4)	
BMI (kg/m^2)	28.8±0.1	27.7±0.1	30.4±0.1	31.8±0.2	33.0±0.5	<0.001
<25.0	30.5 (29.0-31.9)	37.7 (36.5-38.9)	20.3 (18.6-22.0)	12.6 (11.3-13.9)	11.0 (7.5-14.4)	
25.0−29.9	32.6 (31.2-34.0)	31.8 (30.8-32.8)	34.7 (32.8-36.6)	34.2 (32.2-36.2)	24.0 (17.9-30.0)	
≥30	35.1 (33.5-36.8)	28.8 (27.8-29.7)	42.9 (41.0-44.9)	51.2 (49.0-53.4)	62.3 (55.2-69.4)	
Physical activity (%)						0.020
Non sedentary behavior	21.7 (20.5-22.9)	21.5 (20.6-22.4)	21.3 (19.4-23.3)	22.2 (20.4-23.9)	33.2 (26.6-39.8)	

(*Continued*)

Table 1 (*Continued*)

Characters	Total (n=23413)	Group 1 (< 6.0) (n=15435)	Group 2 (6.0-6.7) (n=3828)	Group 3 (6.8-9.0) (n=3801)	Group 4 (>9.0) (n=349)	P-value
Sedentary behavior	78.3 (75.3-81.3)	78.5 (77.6-79.4)	78.7 (76.8-80.6)	77.8 (76.1-79.6)	66.8 (60.2-73.4)	
Smoking status (%)						<0.001
Never smoked	53.7 (51.6-55.8)	55.8 (54.5-57.2)	49.9 (47.6-52.2)	49.2 (47.2-51.3)	46.8 (39.4-54.2)	
Former smoker	25.6 (24.1-27.1)	23.0 (22.0-24.1)	28.6 (26.9-30.4)	32.2 (30.1-34.2)	38.6 (30.9-46.3)	
Current smoker	20.6 (19.4-21.9)	21.1 (19.9-22.2)	21.5 (19.7-23.2)	18.5 (16.9-20.2)	14.5 (9.7-19.3)	
Alcohol intake (%)						<0.001
Non-drinkers	10.1 (9.2-11.0)	11.0 (10.1-11.9)	9.2 (7.7-10.6)	7.6 (6.5-8.7)	9.7 (5.3-14.1)	
Moderate-drinkers	32.4 (30.6-34.1)	31.8 (30.4-33.3)	32.8 (30.8-34.9)	34.7 (32.5-37.0)	24.7 (18.9-30.5)	
Heavy drinkers	40.3 (38.5-42.0)	39.6 (38.2-40.9)	41.1 (38.9-43.4)	41.8 (39.8-43.9)	45.2 (37.7-52.8)	
Stroke (%)	3.1 (2.7-3.4)	2.7 (2.3-3.1)	2.8 (2.3-3.4)	4.2 (3.5-5.0)	10.4 (6.7-14.1)	<0.001
Hypertension (%)	36.6 (34.9-38.2)	30.8 (29.7-31.9)	41.5 (39.4-43.6)	52.4 (50.2-54.7)	70.5 (61.9-79.1)	<0.001
Diabetes (%)	13.0 (12.3-13.7)	11.0 (10.3-11.7)	14.7 (13.2-16.2)	17.5 (16.0-19.0)	38.2 (31.3-45.2)	<0.001
Hyperlipidemia (%)	71.6 (68.7-74.5)	67.5 (66.3-68.6)	77.6 (75.9-79.3)	81.2 (79.5-82.9)	86.8 (81.0-92.7)	<0.001
CKD (%)	14.9 (14.1-15.7)	11.5 (10.8-12.2)	17.0 (15.5-18.5)	23.9 (22.4-25.5)	50.6 (43.8-57.4)	<0.001
CHD (%)	3.5 (3.1-3.9)	2.8 (2.4-3.1)	3.7 (3.0-4.4)	5.5 (4.5-6.5)	13.4 (8.6-18.3)	<0.001
Cancer (%)	9.4 (8.7-10.1)	9.2 (8.5-9.9)	8.8 (7.7-9.9)	10.7 (9.6-11.8)	10.7 (6.8-14.6)	0.060
Antihypertensive (%)	8.1 (7.5-8.8)	6.0 (5.4-6.5)	9.4 (8.1-10.7)	14.4 (12.8-15.9)	25.5 (19.8-31.1)	<0.001
Antihyperlipidemic (%)	16.9 (15.9-18.0)	15.0 (14.1-15.9)	19.5 (17.7-21.2)	21.2 (19.7-22.7)	28.4 (21.9-34.9)	<0.001
Antidiabetic (%)	8.0 (7.5-8.6)	6.8 (6.3-7.4)	8.8 (7.5-10.1)	10.6 (9.4-11.8)	29.2 (22.6-35.9)	<0.001
Antiplatelet (%)	2.5 (2.2-2.8)	2.0 (1.7-2.3)	2.6 (2.1-3.2)	4.2 (3.4-4.9)	7.9 (4.5-11.3)	<0.001
Anticoagulants (%)	2.0 (1.8-2.3)	1.5 (1.3-1.8)	2.3 (1.8-2.8)	3.3 (2.7-4.0)	7.0 (3.6-10.4)	<0.001
Antigout (%)	1.8 (1.6-2.0)	1.4 (1.2-1.7)	1.8 (1.3-2.2)	3.0 (2.3-3.7)	6.9 (3.7-10.2)	<0.001
Corticosteroids (%)	1.2 (1.1-1.4)	1.3 (1.1-1.5)	1.2 (0.7-1.6)	1.0 (0.7-1.3)	0.9 (-0.4-2.2)	0.880
Diuretic (%)	11.9 (11.1-12.7)	8.0 (7.3-8.6)	14.4 (13.0-15.8)	22.8 (21.2-24.4)	48.2 (40.6-55.8)	<0.001
SBP (mmHg)	121.2±0.2	119.3±0.2	123.6±0.4	125.8±0.4	127.9±1.4	<0.001
DBP (mmHg)	70.2±0.2	69.3±0.2	71.2±0.3	72.9±0.3	68.8±1.1	<0.001
UA (mg/dL)	5.5±0.0	4.7±0.0	6.3±0.0	7.5±0.0	9.9±0.1	<0.001
sALB (g/L)	42.3±0.1	42.1±0.1	42.8±0.1	42.8±0.1	41.9±0.3	<0.001
sCr (umol/L)	77.0±0.3	71.7±0.3	83.2±0.6	89.7±0.7	110.6±2.9	<0.001
BUN (mmol/L)	4.8±0.0	4.5±0.0	5.1±0.0	5.6±0.1	7.5±0.3	<0.001
eGFR (mL/min/1.73m^2)	89.6±0.3	92.7±0.4	86.4±0.5	81.6±0.5	67.3±2.1	<0.001
uALB (mg/L)	35.2±1.8	24.3±1.8	37.2±4.0	68.5±6.2	159.4±37.5	<0.001
uCr (mg/dL)	129.4±0.9	121.5±1.1	141.3±1.7	148.7±1.7	141.5±6.1	<0.001
Albumin−creatinine ratio (mg/g)	33.1±1.8	23.9±1.7	33.4±3.9	61.5±5.9	158.4±43.5	<0.001
Glu (mmol/L)	5.8±0.0	5.8±0.0	5.9±0.0	6.0±0.0	6.5±0.1	<0.001
HbA1C (%)	5.6±0.0	5.6±0.0	5.6±0.0	5.7±0.0	6.0±0.1	<0.001

Table 1 (*Continued*)

Characters	Total (n=23413)	Group 1 (< 6.0) (n=15435)	Group 2 (6.0-6.7) (n=3828)	Group 3 (6.8-9.0) (n=3801)	Group 4 (>9.0) (n=349)	P-value
TC (mg/dL)	194.4±0.5	193.1±0.5	196.1±1.0	198.0±1.1	197.0±3.9	<0.001
TG (mg/dL)	129.9±1.1	116.4±1.2	143.5±2.1	165.9±3.5	201.6±15.1	<0.001
LDL-C (mg/dL)	115.3±0.4	113.6±0.4	118.6±0.8	118.6±0.9	113.3±2.4	<0.001
HDL-C (mg/dL)	53.7±0.2	56.5±0.2	49.2±0.3	47.5±0.3	45.8±1.0	<0.001
TB (umol/L)	11.8±0.1	11.3±0.1	12.5±0.1	13.2±0.1	12.8±0.5	<0.001
ALT (U/L)	25.2±0.2	22.5±0.2	29.2±0.8	31.7±0.5	32.4±1.9	<0.001
AST (U/L)	24.7±0.1	23.3±0.1	26.3±0.3	28.2±0.4	31.0±2.1	<0.001
WBC (× 10^9/L)	6.8±0.0	6.7±0.0	7.0±0.1	7.0±0.1	7.8±0.2	<0.001
NEUT (× 10^9/L)	4.0±0.0	4.0±0.0	4.1±0.0	4.1±0.0	4.7±0.1	<0.001
LYM (× 10^9/L)	2.0±0.0	2.0±0.0	2.1±0.0	2.1±0.0	2.1±0.1	<0.001
PLT (× 10^9/L)	250.3±0.8	253.0±0.9	246.0±1.5	243.8±1.5	244.4±4.8	<0.001
HGB (g/dL)	14.4±0.0	14.1±0.0	14.8±0.0	15.0±0.0	14.5±0.1	<0.001
RDW (%)	13.1±0.0	13.1±0.0	13.0±0.0	13.1±0.0	13.6±0.1	<0.001

Values are weighted means ± standard error or weighted % (95% confidence interval). P values are weighted.

NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; CKD, chronic kidney disease; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, uric acid; sALB, serum albumin; sCr, serum creatinine; BUN, urea nitrogen; eGFR, estimated glomerular filtration rate; uALB, urinary albumin; uCr, urine creatinine; Glu, fasting blood glucose; HbA1C, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; NEUT, neutrophil cell count; LYM, lymphocyte cell count; PLT, platelet count; HGB, hemoglobin; RDW, red blood cell distribution width.

[a]Other races contain Non-Hispanic Asian participants and other non-Hispanic race (including non-Hispanic multiracial).

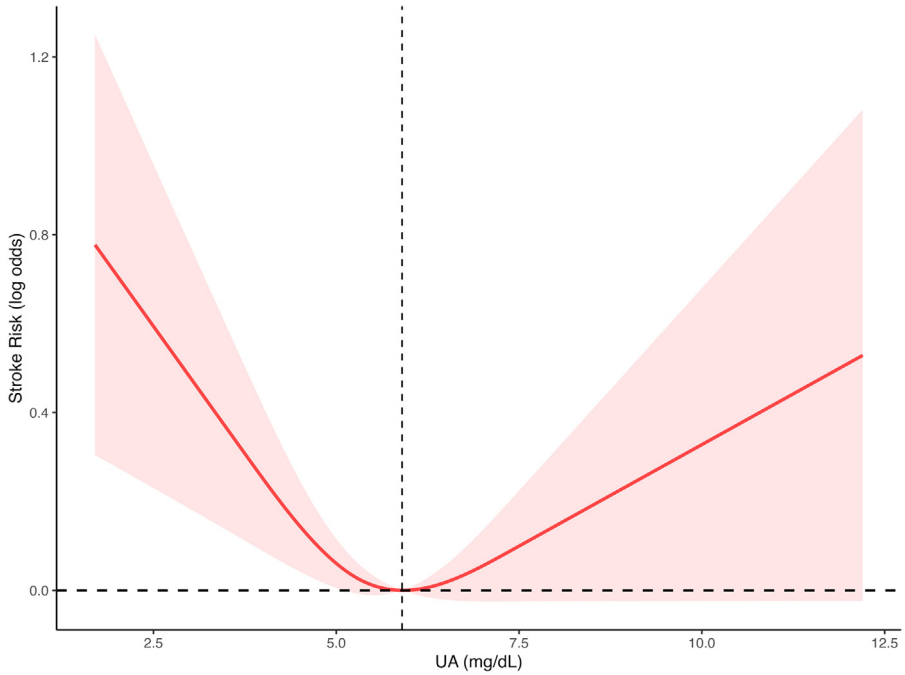

Fig. 2. *The restricted cubic spline for the association of UA and stroke risk.*
Abbreviation: UA, uric acid.

Discussion

Using two decades of NHANES data, our investigation verified a J-type nonlinear relationship between SUA levels and stroke risk; lower and higher SUA levels were statistically associated with increased stroke risk in certain population groups. Elevated SUA levels (SUA 6.8−9.0 mg/dL) showed a protective role in other Hispanic populations. These discoveries may have significant real-world ramifications for stroke prevention.

A meta-analysis[26] revealed that the elevated risk of adult stroke was primarily associated with increased UA levels, showing a J-shaped trend. Our findings are consistent with it and support the notion that increased UA levels are an important risk factor for adult stroke. Another meta-analysis[27] also showed a nonlinear relationship between UA levels and stroke risk but found no effects of UA levels on stroke risk in the US population, contrary to the studies from other locations. Including only a few American studies in the meta-analysis may explain these conflicting results. This lack of relevant research may be overcome using large sample data from the nationally representative American population, as we did in our study.

Our study showed that in addition to high SUA levels, low SUA levels might also increase stroke risk, which was related to UA's dual role (oxidant and antioxidant).[28] Conversely, UA promotes oxidative stress, inflammatory response, and endothelial dysfunction in the plasma, which promotes atherosclerosis. High UA levels enhance this effect and contribute to an increased risk of stroke.[8, 11, 29] However, by decreasing the synthesis of nitric oxide and increasing oxidative stress, low SUA levels may contribute to vascular endothelial dysfunction, thereby promoting stroke. Additionally, decreased cellular UA levels might be related to loss-of-function mutations affecting the UA transporter 1 (encoded by the *SLC22A12* gene) expressed in the kidneys and blood vessels.[8, 30]

Additionally, our research suggests that higher and lower SUA levels increase stroke risk among non-Hispanic whites, while higher SUA levels exert a protective effect on other Hispanic populations. However, this racial disparity is inconsistent with the results from previous studies. The REGARDS study[31] indicated that moderate UA levels might lead to higher stroke risk in Caucasians compared to African Americans, possibly because of geographical and ethnic differences. However, because of lower stroke counts in the Caucasian group, conclusions regarding racial differences could not be drawn. The ARIC study[32] did not reveal race-related differences in stroke risk associated with hyperuricemia among the American population; differences in the research participants may explain this discrepancy because ethnic differences were studied only among those not taking diuretics. Nevertheless, containing five standard racial categories, our sample was representative of the entire adult population in the United States, making our study more comprehensive and clinically significant.

The significant interaction between smoking status and CKD and SUA levels was found in the full adjustment model of our study. This result indicates that the risk

Table 2. *Associations between SUA levels and stroke risk of the overall participants*

	Stroke	Model 1 OR (95% CI), P	Model 2 OR (95% CI), P	Model 3 OR (95% CI), P
Grouping of SUA, (mg/dL)	**n = 910**			
Group 1 (< 6.0)	160	0.95(0.74-1.21) 0.677	1.01(0.79-1.30) 0.918	1.17(0.92-1.48) 0.202
Group 2 (6.0-6.7)	504	Reference	Reference	Reference
Group 3 (6.8-9.0)	202	1.52(1.16-2.00) 0.003	1.39(1.05-1.83) 0.022	1.16(0.86-1.58) 0.333
Group 4 (>9.0)	44	3.99(2.53-6.28) <0.001	2.73(1.72-4.32) <0.001	1.66(1.00-2.74) 0.049
P trend [a]		<0.001	<0.001	<0.001
Sensitivity analysis after exclusion of participants with antigout (None, n = 478)				
Grouping of SUA, (mg/dL)	**n = 853**			
Group 1 (< 6.0)	152	0.95(0.74-1.22) 0.708	1.01(0.78-1.29) 0.970	1.15(0.91-1.46) 0.248
Group 2 (6.0-6.7)	474	Reference	Reference	Reference
Group 3 (6.8-9.0)	186	1.47(1.12-1.95) 0.007	1.33(1.01-1.76) 0.046	1.08(0.79-1.47) 0.634
Group 4 (>9.0)	41	4.38(2.75-6.95) <0.001	2.96(1.85-4.74) <0.001	1.70(1.00, 2.88) 0.0498
P trend [a]		<0.001	<0.001	<0.001

Model 1: Non-adjusted model.

Model 2 adjusted for: sex; age; race.

Model 3 adjusted for: sex; age; race; body mass index; physical activity; smoking status; alcohol intake; coronary heart disease; hypertension; diabetes; hyperlipidemia; chronic kidney disease; antiplatelet; anticoagulants; antigout and red blood cell distribution width.

UA, uric acid; OR, odds ratio; 95% CI, 95% confidence interval.

[a]Test for trend based on variable containing median value for each group.

effect of UA on stroke is different under different smoking and CKD statuses. First, UA levels showed a negative association with smoking; ex-smokers have the highest UA levels, followed by never-smokers and present smokers.[33-35] In our study, low and high levels of UA equally increased stroke risk among former smokers of the overall population, while ex-smokers and non-smokers with high SUA levels increased stroke risk among those aged ≥ 50 years. The reason is that UA is a significant free radical scavenger within the cell during metabolic stress (such as smoking). Cigarette smoke contains superoxide and other active oxygen substances that reduce the serum level of antioxidants.[36] Therefore, the SUA levels of smokers were significantly reduced owing to the reduction in endogenous UA production caused by long-term exposure to cigarette smoke.[34] However, after smoking cessation, SUA levels of former smokers increased because of weight increase and alcohol consumption of varying degrees. UA levels in non-smokers are higher than in smokers.[35] Therefore, higher UA levels might be associated with higher stroke risks in ex-smokers and never-smokers but not in current smokers. Second, CKD is a stand-alone risk factor for stroke. Stroke risk was 4−10 times higher in individuals with end-stage kidney disease getting renal replacement treatment than in the general population.[37] However, we failed to detect an association between CKD and stroke risk at the different SUA levels. Conversely, among patients without CKD, only those with SUA < 6.0 mg/dL had an increased risk of stroke. In hypouricemia, the risk of renal function decline might increase because of a decline in UA antioxidant capacity[38], leading to increased oxidative stress and stroke risk.

In addition to the large sample size and national representativeness, one of the strengths of this study includes the detailed classification of UA levels to provide evidence for clinical practice. In previous studies on the connection between hyperuricemia and stroke, UA levels were generally categorized as < 6.8 mg/dL and ≥ 6.8 mg/dL. However, the US Gout Guideline recommends UA levels < 6.0 mg/dL as the therapeutic target and states that those with significantly higher UA levels (UA > 9.0 mg/dL) tend to experience gout progression.[9] Therefore, our research is suitable for clinical practice as 6.0 mg/dL, 6.8 mg/dL, and 9.0 mg/dL were all used as UA-level cut-offs. Another strength of our study is that it provides a basis for future comparative studies between diuretic users and non-users. UA is an independent predictor of ischemic stroke only in diuretic non-users[5]. The increase in SUA levels caused by diuretic use might benefit the cardiovascular system.[39] However, comparative studies on the correlation between UA and stroke in diuretic users and non-users are currently lacking. Our study found diuretic users had a significantly increased risk of stroke only when SUA levels exceeded 9 mg/dL.

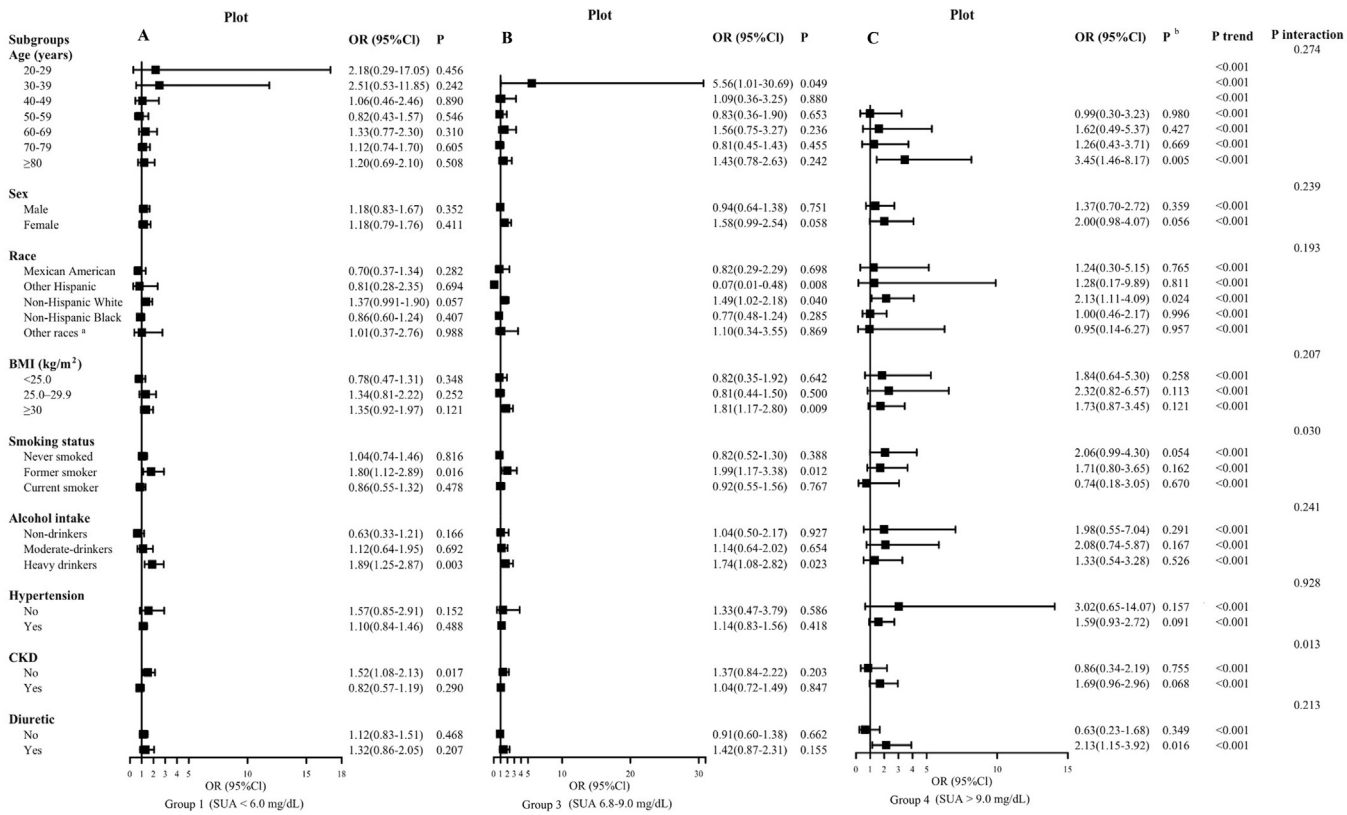

Fig. 3. *Subgroup and interaction analysis of associations between SUA levels and stroke risk of the overall participants in the full adjustment model.*

A, Group 1 (SUA < 6.0 mg/dL); B, Group 3 (SUA 6.8−9.0 mg/dL); C, Group 4 (SUA > 9.0 mg/dL).

Abbreviation: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; SUA, Serum Uric Acid.

Full adjustment model adjusted for: sex; age; race; body mass index; physical activity; smoking status; alcohol intake; coronary heart disease; hypertension; diabetes; hyperlipidemia; chronic kidney disease; antiplatelet; anticoagulants; antigout and red blood cell distribution width. Using Group 2 (SUA 6.0−6.7 mg/dL) as a reference.

[a] Other races contain Non-Hispanic Asian participants and other non-Hispanic race (including non-Hispanic multiracial).

[b] Test for trend based on variable containing median value for each group.

In contrast to non-users, there was no discernible difference in stroke risk among diuretic users when UA levels were slightly or moderately elevated. Moreover, there are also some limitations to our study. Firstly, it could not distinguish between stroke types, such as ischemic or hemorrhagic stroke, or between the first occurrence and recurrence of stroke because the NHANES questionnaire did not make these distinctions. Secondly, there was no independent Asian group data in the subgroup analyses as the NHANES data have only been available for Asians separately since 2011, while our study included data from 1999−2020. Thirdly, because of this study's cross-sectional design, it could only probe into associations without identifying causality.

Conclusions

This study revealed a J-shaped relationship between SUA levels and stroke risk. Moreover, low and high SUA levels were risk factors for stroke in different populations, except for the other Hispanic population. Early intervention and management of SUA levels in high-risk populations, such as Non-Hispanic whites, obesity, ex-smokers, heavy drinkers, diuretic users, and individuals with advanced age and without CKD, are of great important clinical and public health implications for stroke prevention. High-quality evidence support will require further research.

Data Availability

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yun Bao reports financial support was provided by Science and Technology Department of Gansu Province. Jie Shi reports financial support was provided by Science and Technology Department of Gansu Province.

CRediT authorship contribution statement

Bei Gao: Conceptualization, Methodology, Software, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Yun Bao:** Methodology, Formal analysis, Data curation, Funding acquisition, Writing – review & editing. **Min Meng:** Formal analysis, Validation, Writing – review & editing. **Lijun Yu:** Formal analysis, Validation, Writing – review & editing. **Yali Lu:** Formal analysis, Data curation, Writing – review & editing. **Rina Sa:** Formal analysis, Data curation, Writing – review & editing. **Xiaoyan Liang:** Writing – review & editing. **Jie Shi:** Conceptualization, Investigation, Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2023.107206.

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