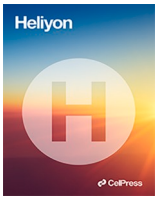
Heliyon 10 (2024) e27169

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Association between serum uric acid and cardiovascular fitness among US adults: A cross-sectional study

Liping Lu [a,1], Xilin Wu [b,*,1], Jiaxin Zhong [a], Qin Chen [a], Huizhong Lin [a], Yukun Luo [a,**]

[a] Department of Cardiology, Fujian Medical University Union Hospital, Fuzhou, Fujian, 350001, China
[b] Department of Neurology, Fujian Medical University Union Hospital Fujian Key Laboratory of Molecular Neurology, Fuzhou, Fujian, 350001, China

ARTICLE INFO

Keywords:
Serum uric acid (SUA)
Heart rate recovery
Cardiovascular fitness
Exercise

ABSTRACT

Background: While serum uric acid (SUA) is known as a cardiovascular disease risk factor and is associated with increased cardiovascular mortality, the relationship between SUA and cardiovascular adaptability under exercise stress remains unclear.
Aims: This study aims to elucidate the relationship between SUA levels and cardiovascular fitness, particularly as manifested during cardiopulmonary exercise testing.
Methods: Utilizing data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004, this study included 5765 participants aged 12–49 years. Heart rate recovery (HRR) during cardiopulmonary exercise testing was measured as an indicator of cardiovascular fitness. Multivariate linear regression analysis was used to explore the association between SUA levels and heart rate recovery at 1 min (HRR1) and 2 min (HRR2) post-exercise.
Results: After adjusting for potential confounders, an inverse relationship was found between SUA levels and both HRR1 and HRR2. Multivariate adjusted smoothing spline plots demonstrated a decrease in HRR1 and HRR2 with increasing SUA levels. This negative correlation was observed across nearly all subgroups.
Conclusions: Elevated SUA levels are indicative of poorer cardiovascular adaptability in the adult US population.

Uric acid is the final products of purine nucleotide metabolism, formed through the oxidation of xanthine and hypoxanthine by xanthine oxidase [1]. Recently, the increasing incidence of hyperuricemia has garnered considerable attention [2]. Epidemiological studies have indicated that elevated serum uric acid (SUA) levels are a strong independent risk factor for cardiovascular diseases [3]. However, the relationship between SUA and cardiovascular fitness under exercise stress remains unclear. In the modern era, the prevalence of cardiovascular diseases is escalating, posing a significant threat to global health. Understanding potential risk factors for cardiovascular diseases is crucial for prevention and management strategies. While the link between SUA levels and cardiovascular health has been extensively studied, the specific mechanisms of this relationship under exercise-induced stress are not well understood. Thus, this study aims to explore the association between SUA levels and cardiovascular adaptability during exercise stress, seeking to

* Corresponding author.
** Corresponding author. Fujian Medical University Union Hospital, NO.29 Xin Quan Road, Fuzhou, Fujian, 350001, China.
E-mail addresses: xlwu@fjmu.edu.cn (X. Wu), luoyukun@fjmu.edu.cn (Y. Luo).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e27169
Received 6 March 2023; Received in revised form 24 January 2024; Accepted 26 February 2024
Available online 27 February 2024

bridge this gap in knowledge. Through this research, we hope to provide new insights into the prevention and intervention of cardiovascular diseases.

To investigate the correlation between SUA and cardiovascular fitness upon an exercise stress, a population based cross-sectional study was perform using data from the National Health and Nutrition Examination Survey (NHANES) in which eligible participants were subjected to a treadmill test. Heart rate recovery after the treadmill test was calculated as a read out for cardiovascular fitness.

1. Methods

1.1. Study participants

Study participants were selected from the noninstitutionalized civilian resident population of the United States who participated in the National Health and Nutrition Examination Survey (NHANES) during the 1999–2004 cycle. The NHANES, a continuous and ongoing annual survey since 1999, periodically focuses on different health indicators each year. Our study specifically utilized the 1999–2004 dataset due to the inclusion of the Treadmill test, a unique feature of this cycle, which is integral to our research objectives. Conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention/Centers for Disease Control and Prevention (CDC), the NHANES aims to assess the health and nutritional status of the United States, releasing its data in 2-year cycles to the public domain. (available on the web at http://www.cdc.gov/nchs/nhanes.htm). The data used a complex, stratified, multistage probability sampling design to attain a nationally representative sample. Participation in the survey is confidential, voluntary and selected participants will receive a personal interview with a standardized physical examination. NHANES protocols and procedures were agreed by the National Center for Health Statistics Research ethics review board, and written informed consent was obtained from all participants.

From NHANES 1999–2004, a total of 31126 volunteers were selected at the examination center. The NHANES comprises two components: one is the interview and the other is the physical examination. Before the examination, questionnaires are administered, followed by the collection of blood samples and treadmill testing. To ensure the safety and validity of the test, survey participants aged 12–49 years old are eligible for the treadmill test (based on data from the Aerobics Center Longitudinal Study). Since only individuals who were fasting were eligible for uric acid testing, and only participants aged 12 to 49 qualified for the cardiovascular health treadmill test, we ultimately selected participants who completed the uric acid testing and were within the 12–49 age range as our study subjects. Adolescents were excluded because the autonomic nervous system function in adolescents differs from that in adults [4, 5]. Participants are excluded if they are taking medications (such as antiarrhythmics, beta blockers). We excluded 28158 participants because of one or more of the following reasons: participants <18 years old, >49 years old (n = 21558); physical functioning limitations(n = 816); cardiovascular conditions(n = 590); lung/breathing conditions(n = 247); asthma symptoms(n = 161); usage of vasoactive medication(n = 95); other specific reasons(n = 224); pregnancy >12 weeks(n = 657); subject's refusal(n = 127); inadequate time(n = 648); technical problems(n = 1289); priority 1 stopping criteria(participant discomfort or distress observed by the health technician or reported by the participant that warranted an emergency stop of the protocol,n = 88); priority 2 stopping criteria (safety concerns arose during the test that warranted an early stop of the protocol, n = 844); not being able to calculate maximal

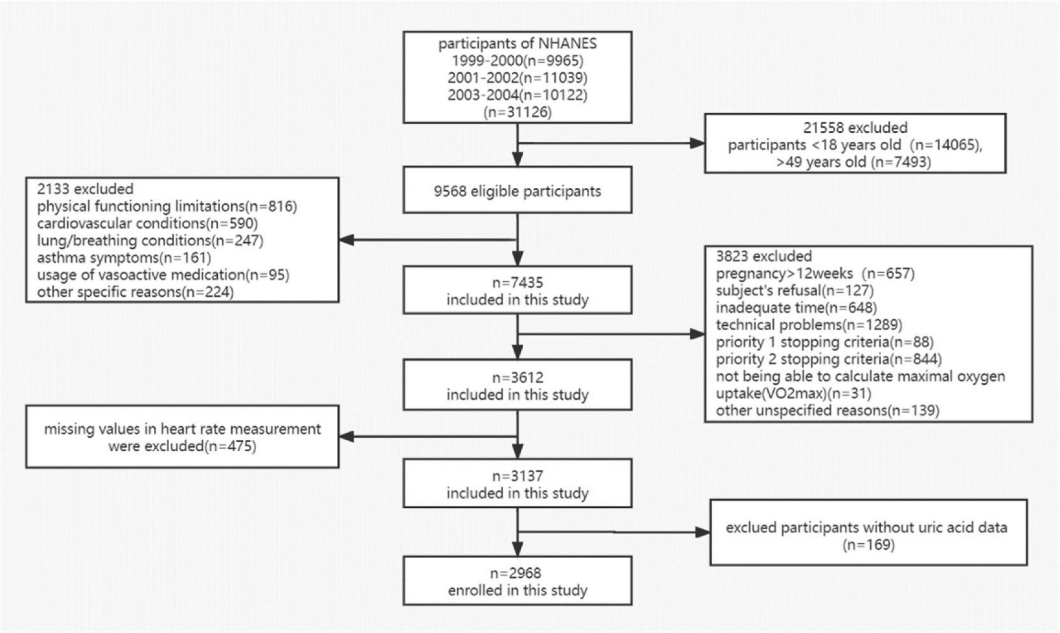


Fig. 1. Flow chart of Study Participants Selection.

oxygen uptake(VO_2max)(n = 31); other unspecified reasons(n = 139); missing values in heart rate measurement(n = 475); missing uric acid(n = 169).Eventually, 2968 participants were included in the final study (Fig. 1).

1.2. Treadmill test

The treadmill test protocol is based on age, gender, BMI, and self-reported level of physical activity, participants were assigned to one of eight protocols. Each protocol includes a 2-min warm-up, two 3-min exercise stages, and a 2-min cool down period (https://wwwn.cdc.gov/nchs/data/nhanes/2003-2004/manuals/cv_99-04.pdf). The primary goal of the exercise test was to achieve a sub-maximal exercise effect, with the target heart rate (HR) reaching approximately 75% of the age-predicted maximum (calculated as 220 minus the participant's age) by the end of the exercise. To assess the participants' cardiac response to exercise, we focused on measuring Heart Rate Recovery (HRR) at two specific time points: HRR1 (Heart Rate Recovery at 1 min): This is calculated as the difference between the peak heart rate achieved during the exercise and the heart rate measured 1 min into the recovery period. HRR1 reflects the speed at which the heart rate begins to return to its resting state, providing an indication of the autonomic nervous system's ability to modulate cardiac function post-exercise. Similarly, HRR2 (Heart Rate Recovery at 2 min) is the decrease in heart rate from its peak value during exercise to the heart rate 2 min after the cessation of exercise. HRR2 offers additional insight into the continued recovery process and the body's return to a resting state. An automated monitoring system was used for continuous HR recording during each stage of the exercise. The data collected on HRR1 and HRR2 allowed us to precisely evaluate the cardiovascular and autonomic responses of the participants to submaximal exercise, which are crucial for understanding cardiovascular fitness and health.

1.3. SUA measurement

SUA levels were measured with a Hitachi 917 automated analyzer (Roche Diagnostics, Indianapolis, IN, USA) or a Beckman Synchron LX20(Beckman Coulter, Inc, Brea, CA, USA) after oxidized by uricase to allantoin and hydrogen peroxide(H_2O_2).

1.4. Major variables

The major variables in this study include gender(male, female), age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other race), Body Mass Index(BMI,normal: below 25 kg/m^2; overweight: 25–30 kg/m^2;obesity:≥30 kg/m^2), educational level (below high school, high school, and above high school),alcohol consumption (having at least 12 alcohol drinks per year or not), smoking status(smoking at least 100 cigarettes in life or not), physical activity(vigorous activity over past 20 days), hypertension, diabetes, total cholesterol (TC), triglycerides(TG), serum creatinine (Cr), diuretics(taken in the past month, including allopurinol, antihypertensives, and probenecid), peak HR (peak heart rate during exercise test).BMI was calculated by dividing the weight (kg) by height squared (m^2). Hypertension was defined as self-reported diagnosis of hypertension by a physician or use of antihypertensive medication. Diabetes was defined as self-reported diagnosis of diabetes by a physician or use of anti-diabetic medications.

1.5. Statistical analysis

All statistical analyses were conducted using statistical packages R (http://www.R-project.org;version 3.4.4) and EmpowerStats (http://www. empowerstats.com , X&Y solutions, inc. Boston, Massachusetts). We defined statistical significance as p-value < 0.05. To assure national representation, we used weighted analyses as recommended by the analytical guidelines of the NCHS (https://wwwn.cdc.gov/nchs/data/nhanes/analyticguidelines/99-10-analytic-guidelines.pdf). We employ the method of quartile analysis to categorize serum uric acid levels into four quartiles, considering the lowest quartile as the comparison group. The continuous variables were presented as median (interquartile range) or mean (standard deviation). Covariates were compared among four groups with differing HRR levels. The categorical variables were characterized by percentage. Associations of serum uric acid and HRR1 or HRR2 were evaluated by multivariable linear regression models. Following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement guidelines [6],we used three models with progressive degrees of adjustment. Firstly, we conducted analyses adjusting for age (continuous variable), gender (male, female), and race (categorical variable). Subsequently, we adjusted for factors including education level (below high school, high school, above high school), alcohol consumption (categorical variable), smoking status (categorical variable), hypertension(yes/no), diabetes(yes/no) and BMI (continuous variable). Finally, we further adjusted for TC (continuous variable), TG (continuous variable), Cr (continuous variable), estimated VO2max (continuous variable), peak HR (continuous variable), diuretics (categorical variable), physical activity (categorical variable). In additional stratified analyses, possible modifications of the association between SUA and HRR1 or HRR2 were also assessed for the following variables: age (18≤age≤20,21≤age≤33,34≤age≤49), gender(male, female), race(Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, Other race), BMI(< 25,25≤BMI<30,≥30). The smooth curve fittings were further performed to explore their potential nonlinear relationships. Covariates were chosen based on some published studies [7,8]. In this study, we addressed the issue of missing data by employing a mean substitution method. Wherever data points were absent, we calculated the mean value of the available data for that specific variable and used this mean value as a substitute.

2. Results

Overall,2968 participants aged 18–49 were included in this study and categorized into 5 racial groups: Non-Hispanic White (n = 1277), Non-Hispanic Black (n = 611), Mexican American (n = 832), Other Hispanic (135), Other race (n = 113). The mean age was 29.02 ± 9.73 years, mean HRR1 was 11.19 ± 7.15, mean HRR2 was 29.61 ± 11.55, mean SUA level was 5.14 ± 1.35 mg/dL. The SUA levels were categorized based on quartiles: Q1(1.40–4.00), Q2(4.10–4.80), Q3(4.90–5.80), Q4(5.90–14.90). Baseline characteristics of participants among different SUA levels were shown in Table 1. As the serum uric acid levels gradually increased, the proportion of males, BMI, Cr, TC, TG, history of hypertension, use of diuretic drugs, alcohol consumption ratio, physical activity, HRR1, HRR2, and peak HR also showed an upward trend.

The smoothing curve showed that, after adjusting for sex, age, smoking status, alcohol consumption, BMI, hypertension, and diabetes, estimated VO_2max, diuretics, peak HR, physical activity, TC, TG, Cr, there is an inverse linear correlation between SUA and

Table 1
Weighted characteristics of NHANES 1999–2004 participants 18–49 years of age.

Characteristics		Serum uric acid(mg/dL)				
	Overall	Q1 (1.40–4.00)	Q2 (4.10–4.80)	Q3 (4.90–5.80)	Q4 (5.90–14.90)	p-value
Number of subjects	2968	672	802	747	747	<0.0001
Age (year)	32.43 ± 9.23	33.41 ± 9.12	32.48 ± 9.36	32.70 ± 9.30	31.19 ± 9.00	<0.0001
Gender (%)						<0.0001
Male	50.29	5.30	33.83	70.92	88.36	
Female	49.71	94.70	66.17	29.08	11.64	
Race (%)						0.0266
Mexican American	9.43	8.48	9.26	9.82	10.09	
Other Hispanic	5.86	6.34	7.01	6.52	3.57	
Non-Hispanic White	70.49	73.37	67.80	70.32	70.76	
Non-Hispanic Black	9.46	8.89	11.05	8.31	9.52	
Other Race	4.75	2.92	4.88	5.03	6.05	
Education (%)						<0.0001
Below high School	15.29	13.63	16.94	15.47	14.95	
High School	25.41	20.09	23.38	30.07	27.77	
Above high School	59.14	65.97	59.68	54.12	57.28	
Not recording	0.16	0.32	–	0.34	–	
Had at least 12 alcohol drinks 1 year						0.0579
Yes	21.39	20.61	21.86	21.09	21.95	
No	5.63	7.56	6.56	4.52	3.98	
Not recording	72.98	71.83	71.57	74.39	74.07	
Current smoking (%)						<0.0001
Yes	29.37	23.31	28.60	34.47	30.66	
No	16.98	16.57	15.93	18.21	17.21	
Not recording	53.65	60.12	55.47	47.32	52.13	
Hypertension (%)						<0.0001
Yes	7.85	4.91	6.38	8.06	11.86	
No	91.15	94.88	92.88	90.44	86.62	
Not recording	1.01	0.21	0.74	1.50	1.52	
Diabetes (%)						0.0387
Yes	1.14	1.11	1.26	0.53	1.66	
No	98.20	98.18	97.51	99.47	97.65	
Not recording	0.66	0.71	1.23	–	0.70	
BMI (kg/m^2)	26.28 ± 5.44	23.85 ± 4.34	25.72 ± 5.40	26.60 ± 5.04	28.79 ± 5.66	<0.0001
Creatinine (umol/L)	72.34 ± 16.84	60.52 ± 12.04	69.43 ± 15.65	76.78 ± 16.02	81.90 ± 15.14	<0.0001
Total cholesterol (mg/dL)	189.38 ± 37.67	184.14 ± 33.17	186.99 ± 34.98	189.91 ± 38.47	196.17 ± 42.16	<0.0001
Triglyceride (mmol/L)	1.30 ± 1.04	0.96 ± 0.51	1.16 ± 0.85	1.33 ± 1.00	1.73 ± 1.41	<0.0001
Estimated VO_2max(ml/kg/min)	40.24 ± 9.29	37.19 ± 8.56	39.06 ± 9.71	42.09 ± 9.45	42.43 ± 8.29	<0.0001
Vigorous activity over past 20 days						0.1492
Yes	51.96	48.20	52.29	53.53	53.56	
No	47.89	51.77	47.51	46.47	46.11	
Not recording	0.14	0.03	0.20	–	0.33	
Serum uric acid(mg/dL)	5.14 ± 1.37	3.43 ± 0.44	4.54 ± 0.29	5.52 ± 0.29	6.95 ± 0.77	0.0001
HRR1 (heart beats)	10.76 ± 6.79	9.87 ± 6.61	10.76 ± 6.48	11.12 ± 7.27	11.22 ± 6.69	0.0006
HRR2 (heart beats)	29.22 ± 11.24	27.67 ± 10.77	29.15 ± 11.30	29.89 ± 11.42	30.08 ± 11.27	0.0001
Peak HR (heart beats)	142.58 ± 16.59	139.79 ± 16.13	142.19 ± 16.42	143.15 ± 17.09	145.01 ± 16.27	<0.0001
Diuretics						0.1291
Yes	0.53	0.37	0.89	0.09	0.75	
No	99.47	99.63	99.11	99.91	99.25	

Mean ± SD for continuous variables : age, uric acid(mg/dL), creatinine(umol/L), BMI, total cholesterol(mg/dL), triglyceride(mmol/L), estimated VO2max(ml/kg/min), HRR1, HRR2, peak HR, p value was calculated by weighted linear regression model.
% for categorical variables: gender, race, education, Had at least 12 alcohol drinks 1 year, smoking status, HBP, DM, Diuretics, Vigorous activity over past 20 days, P value was calculated by weighted chi-square test.

HRR1 or HRR2 (Fig. 2a and b) .

In our refined multivariable linear regression analysis, the β coefficients provide valuable insights into the relationship between serum uric acid (SUA) levels and heart rate recovery (HRR1 and HRR2). These coefficients measure the expected change in HRR1 and HRR2 for each one-unit increase in SUA levels, controlling for other variables in the model. For instance, in Model 1, where we adjusted for age, gender, and race, the β coefficient for HRR1 is −0.52, with a 95% confidence interval (CI) of −0.75 to −0.30 and a highly significant p-value (p-value < 0.0001). This implies that for each one-unit increase in SUA, HRR1 decreases by 0.52 units on average, indicating an inverse relationship. The magnitude of this coefficient and its statistical significance suggest a meaningful and robust association. Similarly, for HRR2 in the same model, the β coefficient is −1.78 (95% CI: 2.12 to −1.44, p-value < 0.0001), suggesting an even stronger inverse relationship between SUA levels and HRR2. In Model 2, which includes additional adjustments for BMI, smoking status, alcohol consumption, education level, hypertension, and diabetes, the β coefficients for HRR1 and HRR2 are −0.39 and −0.37, respectively. These values, along with their respective confidence intervals and p-values (HRR1: 95% CI: 0.63 to −0.14, p-value = 0.0019; HRR2: 95% CI: 0.72 to −0.02, p-value = 0.0396), further substantiate the inverse association between SUA levels and heart rate recovery, even when considering a broader range of confounding factors. Similar results were observed in model 3 (adjusted for age, gender, race, BMI, smoking status, alcohol consumption, education, hypertension, diabetes, peak HR, diuretics, estimated VO_2max, physical activity, TC, TG, Cr). The consistent inverse relationship across all models underscores the potential clinical relevance of SUA levels in heart rate recovery post-exercise.

We further explored the stratified analyses of SUA levels associated with HRR1 or HRR2 according to age (categorized based on 3 quartiles), gender, race, BMI by linear regression. Inverse relations between SUA levels and HRR1 or HRR2 were noted for almost all strata (Table 2 and Table 3).

3. Discussion

In this large national, cross-sectional study, we found that SUA level was negatively associated with HRR level, which is a marker of cardiovascular fitness [9]. In stratified analyses, SUA also interacted with HRR. Although we found some non-significant associations between them, the trends were consistent with our multivariable linear regressions. This finding indicated that SUA at a high level may be harmful to healthy autonomic nervous functioning. We also observed some different interactions with SUA levels and HRR1 or HRR2 by race. So far, little is known about the effect of hyperuricemia exposure on cardiovascular fitness upon exercise stress, this is the first study revealing the relationship between SUA and HRR in nationally representative sample.

The mechanisms of SUA and HRR interaction remain unclear, but several possibilities have been proposed. We hypothesize that this interaction is mediated through a complex network involving sympathetic nervous activity, metabolic processes, and hormonal control systems like the renin–angiotensin–aldosterone system (RAAS). This interaction potentially creates a sympathovagal imbalance, characterized by increased sympathetic and decreased parasympathetic activities, leading to abnormal HRR. First, sympathetic nervous activity or norepinephrine can activate uric acid and its precursors (hypoxanthine and xanthine) [10]. In addition, higher SUA levels were associated with greater RAAS activity [11,12], which may further exacerbate this imbalance. This interaction forms a

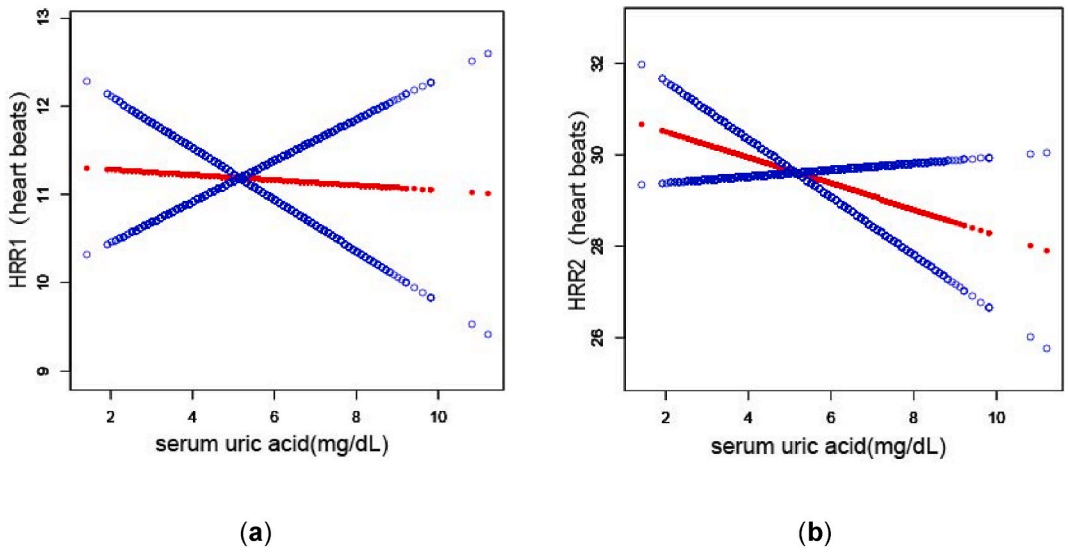


Fig. 2. Multivariate adjusted smoothing curve of HRR by SUA (a to b): (a) Multivariate adjusted smoothing curve of HRR1 by SUA. (b)Multivariate adjusted smoothing curve of HRR2 by SUA. Red dotted lines represent the spline plots of SUA and blue dotted lines represent the 95% CIs of the spline plots. Adjusted for sex, age, smoking status, alcohol consumption, BMI, education, hypertension, and diabetes, peak HR, estimated VO2max, diuretics, physical activity, TC, TG, Cr. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Association of SUA with HRR1 among 18–49 years old participants, NHANES 1999–2004 (weighted) .

	N	Model I		Model II		Model III	
		β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
Uric acid (mg/dL)	2968	−0.52 (−0.75, −0.30)	<0.0001	−0.39 (−0.63, −0.14)	0.0019	−0.31 (−0.56, −0.06)	0.0144
Stratified by Age							
18≤age≤20	919	−0.29 (−0.70, 0.12)	0.1597	−0.35 (−0.79, 0.08)	0.1108	−0.33 (−0.79, 0.12)	0.1505
21≤age≤33	1009	−0.59 (−1.01, −0.17)	0.0065	−0.49 (−0.96, −0.03)	0.0379	−0.41 (−0.88, 0.06)	0.0874
34≤age≤49	1040	−0.54 (−0.89, −0.19)	0.0026	−0.39 (−0.63, −0.14)	0.0524	−0.28 (−0.67, 0.11)	0.1625
Stratified by Gender							
Male	1506	−0.41 (−0.71, −0.11)	0.0078	−0.46 (−0.78, −0.13)	0.0057	−0.33 (−0.66, 0.00)	0.0511
Female	1462	−0.65 (−0.99, −0.31)	0.0002	−0.30 (−0.69, 0.08)	0.1197	−0.33 (−0.72, 0.06)	0.0977
Race							
Mexican American	832	0.24 (−0.20, 0.68)	0.2926	0.61 (0.14, 1.09)	0.0109	0.75 (0.25, 1.25)	0.0033
Other Hispanic	135	−0.37 (−1.46, 0.73)	0.5128	−0.76 (−1.97, 0.45)	0.2195	–	–
Non-Hispanic White	1277	−0.71 (−1.06, −0.36)	<0.0001	−0.61 (−0.99, −0.24)	0.0014	−0.50 (−0.88, −0.11)	0.0112
Non-Hispanic Black	611	−0.26 (−0.77, 0.26)	0.3250	−0.04 (−0.60, 0.53)	0.8995	−0.02 (−0.57, 0.61)	0.9462
Other Race	113	0.17 (−0.78, 1.12)	0.7198	0.14 (−1.07, 1.35)	0.8187	0.26 (−0.99, 1.52)	0.6809
Stratified by BMI							
BMI <25	1479	−0.01 (−0.41, 0.38)	0.9467	−0.05 (−0.44, 0.34)	0.8029	0.02 (−0.42, 0.39)	0.9352
25≤ BMI <30	881	−0.45 (−0.88, −0.03)	0.0374	−0.34 (−0.77, 0.09)	0.1171	−0.35 (−0.79, 0.09)	0.1205
BMI≥30	608	−1.15 (−1.56, −0.73)	<0.0001	−1.05 (−1.47, −0.63)	<0.0001	−0.93 (−1.35, −0.51)	<0.0001

Adjusted covariates: model 1 = age, gender, and race; model 2 = model 1+BMI, hypertension, diabetes, alcohol consumption, smoking status, education; model 3 = model 2+TC, TG, Cr, estimated VO2max(ml/kg/min), peak HR, diuretics, physical activity.

Table 3
Association of SUA with HRR2 among 18–49 years old participants, NHANES 1999–2004 (weighted) .

	N	Model I		Model II		Model III	
		β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
Uric acid (mg/dL)	2968	−1.78 (−2.12, −1.44)	<0.0001	−0.37 (−0.72, −0.02)	0.0396	−0.35 (−0.69, −0.00)	0.0483
Stratified by Age							
18≤age≤20	919	−1.23 (−1.86, −0.60)	0.0002	−0.14 (−0.77, 0.50)	0.6772	−0.15 (−0.81, 0.50)	0.6439
21≤age≤33	1009	−1.59 (−2.18, −1.00)	<0.0001	−0.13 (−0.75, 0.48)	0.6672	−0.16 (−0.75, 0.43)	0.5943
34≤age≤49	1040	−2.08 (−2.65, −1.51)	<0.0001	−0.61 (−1.18, −0.03)	0.0382	−0.50 (−1.07, 0.08)	0.0889
Stratified by Gender							
Male	1506	−1.22 (−1.64, −0.79)	<0.0001	−0.48 (−0.93, −0.04)	0.0326	−0.23 (−0.68, 0.21)	0.3056
Female	1462	−2.49 (−3.04, −1.94)	<0.0001	−0.22 (−0.79, 0.35)	0.4433	−0.55 (−1.09, −0.02)	0.0425
Stratified by Race							
Mexican American	832	−0.94 (−1.60, −0.28)	0.0057	0.21 (−0.47, 0.89)	0.5444	0.10 (−0.59, 0.79)	0.7773
Other Hispanic	135	−1.51 (−3.06, 0.04)	0.0584	−0.42 (−2.12, 1.29)	0.6338	–	–
Non-Hispanic White	1277	−1.79 (−2.32, −1.27)	<0.0001	−0.32 (−0.86, 0.22)	0.2399	−0.26 (−0.79, 0.27)	0.3313
Non-Hispanic Black	611	−2.35 (−3.15, −1.55)	<0.0001	−1.04 (−1.88, −0.20)	0.0161	−0.87 (−1.71, −0.02)	0.0446
Other Race	113	−2.04 (−3.26, −0.81)	0.0015	−1.05 (−2.51, 0.40)	0.1586	−1.11 (−2.60, 0.38)	0.1486
Stratified by BMI							
BMI <25	1479	−0.14 (−0.71, 0.43)	0.6329	−0.10 (−0.67, 0.47)	0.7368	−0.17 (−0.75, 0.40)	0.5553
25≤ BMI <30	881	−0.39 (−0.98, 0.20)	0.2004	−0.27 (−0.86, 0.33)	0.3774	−0.20 (−0.77, 0.37)	0.4906
BMI≥30	608	−1.78 (−2.43, −1.14)	<0.0001	−1.60 (−2.25, −0.95)	<0.0001	−1.26 (−1.85, −0.67)	<0.0001

Adjusted covariates: model 1 = age, gender, and race; model 2 = model 1+BMI, hypertension, diabetes, alcohol consumption, smoking status; model 3 = model 2+ TC, TG, Cr, estimated VO2max(ml/kg/min), peak HR, diuretics, physical activity.

vicious circle, consistently damaging the cardiovascular system [13,14]. Understanding these mechanisms in depth is crucial, as it may reveal new therapeutic targets for improving cardiovascular health in individuals with elevated SUA levels. Further research is needed to investigate these underlying mechanisms.

Oshima [12] suggested that SUA may increase peripheral sympathetic nerve activity through its specific transporters in Wistar rats. However, this observation contrasts with human studies. For instance, in a randomized, placebo-controlled trial, Mcmullan [15] found that uric acid lowering (treated with probenecid or allopurinol) had no effect on systemic RAS activity after 8 weeks. This discrepancy highlights the complexity of SUA's impact on the cardiovascular system and suggests that the effects in humans may require a prolonged period of treatment to become evident, as opposed to the more immediate effects observed in animal models. Recently, a multicenter study suggested that cardiovascular mortality associated with elevated UA was modulated by the level of resting HR, supporting the hypothesis that activation of the sympathetic nervous system facilitates the action of UA as a cardiovascular risk factor [16].

Previous studies have examined the relationship between SUA and autonomic nervous function. In a cross-sectional study of adults aged 18–60 years, Kunikullaya [13] evaluated a significant negative correlation between SUA and autonomic nervous function using Pearson's/Spearman's correlation. This implies that higher SUA levels may be linked to increased sympathetic activity. Another

cross-sectional study expanding these findings to older adults, Passos [14] provided evidence that hyperuricemic older adults show a sympathovagal imbalance when compared to normouricemic older adults, characterized by greater sympathetic predominance and lower vagal modulation at rest conditions. Our findings align with these observations, suggesting a potential role of SUA in modulating autonomic nervous system balance, which could be a crucial factor in cardiovascular health. In a healthy population with a high proportion of overweight and obese participants, Lambert [17] found that SUA is independently and positively associated with measures of sympathetic tone, indicating the potential value of SUA as a marker of early cardiovascular disease development. These insights underscore the importance of our analysis and the need for further large-sample, prospective studies to confirm these associations and unravel the detailed mechanisms linking SUA levels with cardiovascular health. Following the STROBE guideline [6], we performed subgroup analyses to make better use of the data. As a result, we observed that their HRR1 and HRR2 decreased when the SUA level was increased. However, further large-sample prospective studies are needed to confirm this conclusion.

The main strengths of our study are as follows. Firstly, our study is a nationally, large, cross-sectional, representative study, included participants aged 18–49 years among the noninstitutionalized civilian resident population of the United States. Furthermore, this study provided a more reliable result, because of the data using a complex, stratified, multistage probability sampling design to attain a nationally representative sample of indicators. Thus, this large sample size allowed us to perform further subgroup analyses. Therefore, we fully adjusted for potential confounding factors in the exploration of the association between SUA and HRR levels.

However, the limitations are worth noting. Primarily, as a cross-sectional design, it was difficult to determine whether there was a causal relationship between SUA and HRR, further prospective longitudinal studies would be important to support these conclusions. Furthermore, although we adjusted several main covariates in the analysis, the associations reported may partially be due to other potential confusion (for example, other unobserved variables or residual confounding variables). Thirdly, we only collected diuretics which participants taken in the past month, and there are some other medicines may influence HR or SUA were not shown in this study. Furthermore, we did not include individuals older than 50 years in the for the treadmill test for safety concern, this prevents us from investigating the relationship between SUA and HRR in older population. Thus, the role of SUA in autonomic nervous system requires further clarification, and a longitudinal follow-up study with a large sample size will be needed.

In this study, we comprehensively analyzed the relationship between Serum Uric Acid (SUA) levels and Heart Rate Recovery (HRR) as indicators of cardiovascular fitness and autonomic nervous system functionality in the community-dwelling population. Our findings underscore the significance of SUA not only as a biomarker but also as a potential therapeutic target in cardiovascular health. Elevated SUA levels were associated with a diminished HRR, suggesting an adverse impact on the autonomic nervous system's capacity to regulate cardiovascular function. These results imply that management strategies aimed at reducing SUA levels could be beneficial in enhancing cardiovascular fitness and improving autonomic function, particularly in individuals with higher SUA levels. This study contributes to a deeper understanding of the multifaceted role of SUA in cardiovascular health and highlights the need for further research into targeted interventions for optimizing autonomic and cardiovascular function. Further longitudinal follow-up studies should expand our analysis with greater sample, aiming to confirm or refute our findings. This study has made significant contributions to understanding the role of serum uric acid (SUA) as a marker of cardiovascular fitness, particularly in the community-dwelling population. Our analysis reveals a notable association between elevated SUA levels and impaired heart rate recovery (HRR) following exercise, suggesting a potential dampening effect on the autonomic nervous system. This finding is particularly salient as it links hyperuricemia, often considered in metabolic and renal contexts, with cardiovascular and autonomic function.

From a clinical perspective, our results indicate that monitoring and potentially managing SUA levels could be an important aspect of cardiovascular fitness strategies. Specifically, individuals with elevated SUA might benefit from interventions aimed at reducing these levels, thereby possibly enhancing their cardiovascular fitness and autonomic function. This approach could offer a novel angle in the management of cardiovascular health, especially in populations where hyperuricemia is prevalent.

However, it is important to acknowledge the limitations of our study. The cross-sectional nature of our analysis using the NHANES dataset limits our ability to infer causality. While we have identified an association, the direction of this relationship and the underlying mechanisms remain to be fully elucidated. Additionally, the data, being nearly two decades old, may not fully represent the current trends and associations in a contemporary population.

Therefore, we strongly recommend further longitudinal studies with larger and more recent datasets to validate our findings. Such studies should aim to explore the causal relationships and underlying mechanisms between SUA levels, cardiovascular fitness, and autonomic function. Investigating these aspects could provide more definitive evidence and potentially uncover new therapeutic targets for improving cardiovascular health.

In conclusion, our study highlights the potential role of SUA as a valuable marker for cardiovascular fitness and opens up new avenues for research and clinical intervention in the field of cardiovascular health and hyperuricemia management.

Institutional review board statement

The NHANES protocols and procedures was approved by the National Center for Health Statistics Research Ethics Review Board (Protocol #98-12, https://www.cdc.gov/nchs/nhanes/irba98.htm).

Informed consent statement

All participants provided written informed consent prior to the interview and examination (https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Documents.aspx).

Data availability statement

The NHANES database is available at: https://www.cdc.gov/nchs/nhanes/index.htm. The details data described in this study are available from the author on reasonable request.

Funding

This work was supported by Excellent Young Scholars Cultivation Project of Fujian Medical University Union Hospital (2022XH030)

CRediT authorship contribution statement

Liping Lu: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Investigation. **Xilin Wu:** Conceptualization, Funding acquisition, Validation, Writing – original draft, Writing – review & editing, Project administration. **Jiaxin Zhong:** Writing – review & editing. **Qin Chen:** Methodology. **Huizhong Lin:** Writing – review & editing. **Yukun Luo:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

none.

References

[1] J. Maiuolo, F. Oppedisano, S. Gratteri, C. Muscoli, V. Mollace, Regulation of uric acid metabolism and excretion, Int. J. Cardiol. 213 (2016), https://doi.org/10.1016/j.ijcard.2015.08.109.
[2] G. Singh, B. Lingala, A. Mithal, Gout and hyperuricaemia in the USA: prevalence and trends, Rheumatology 58 (12) (2019) 2177–2180, https://doi.org/10.1093/rheumatology/kez196.
[3] M.E. Kleber, G. Delgado, T.B. Grammer, G. Silbernagel, J. Huang, B.K. Krämer, E. Ritz, W. März, Uric acid and cardiovascular Events: a mendelian randomization study, J. Am. Soc. Nephrol. 26 (11) (2015) 2831–2838, https://doi.org/10.1681/ASN.2014070660.
[4] E. Longin, C. Dimitriadis, S. Shazi, T. Gerstner, T. Lenz, S. König, Autonomic nervous system function in infants and adolescents: impact of autonomic tests on heart rate variability, Pediatr. Cardiol. 30 (3) (2009) 311–324, https://doi.org/10.1007/s00246-008-9327-8.
[5] S.B. Mulkey, A.J. du Plessis, Autonomic nervous system development and its impact on neuropsychiatric outcome, Pediatr. Res. 85 (2) (2019) 120–126, https://doi.org/10.1038/s41390-018-0155-0.
[6] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, Lancet 370 (9596) (2007) 1453–1457, https://doi.org/10.1016/S0140-6736(07)61602-X.
[7] Y.J. van de Vegte, P. van der Harst, N. Verweij, Heart rate recovery 10 seconds after cessation of exercise predicts death, J. Am. Heart Assoc. 7 (8) (2018), https://doi.org/10.1161/JAHA.117.008341.
[8] S.Y. Jae, S. Kurl, J.A. Laukkanen, F. Zaccardi, Y.-H. Choi, B. Fernhall, M. Carnethon, B.A. Franklin, Exercise heart rate reserve and recovery as predictors of incident type 2 diabetes, Am. J. Med. 129 (5) (2016), https://doi.org/10.1016/j.amjmed.2016.01.014.
[9] T. Peçanha, N.D. Silva-Júnior, CLdM. Forjaz, Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases, Clin. Physiol. Funct. Imag. 34 (5) (2014) 327–339, https://doi.org/10.1111/cpf.12102.
[10] M. Kaya, Y. Moriwaki, T. Ka, T. Inokuchi, A. Yamamoto, S. Takahashi, Z. Tsutsumi, J. Tsuzita, Y. Oku, T. Yamamoto, Plasma concentrations and urinary excretion of purine bases (uric acid, hypoxanthine, and xanthine) and oxypurinol after rigorous exercise, Metabolism 55 (1) (2006) 103–107, https://doi.org/10.1016/j.metabol.2005.07.013.
[11] M. Mazzali, J. Kanellis, L. Han, L. Feng, Y.-Y. Xia, Q. Chen, D.-H. Kang, K.L. Gordon, S. Watanabe, T. Nakagawa, et al., Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism, Am. J. Physiol. Ren. Physiol. 282 (6) (2002) F991–F997, https://doi.org/10.1152/ajprenal.00283.2001.
[12] N. Oshima, H. Onimaru, H. Matsubara, T. Uchida, A. Watanabe, H. Takechi, Y. Nishida, H. Kumagai, Uric acid, indoxyl sulfate, and methylguanidine activate bulbospinal neurons in the RVLM via their specific transporters and by producing oxidative stress, Neuroscience 304 (2015) 133–145, https://doi.org/10.1016/j.neuroscience.2015.07.055.
[13] K.U. Kunikullaya, N. Purushottam, V. Prakash, S. Mohan, R. Chinnaswamy, Correlation of serum uric acid with heart rate variability in hypertension, Hipertens. Riesgo Vasc. 32 (4) (2015) 133–141, https://doi.org/10.1016/j.hipert.2015.06.001.
[14] R.S. Passos, Í.J.S. Ribeiro, I.V. Freire, M.F. Teles, R.A. Pires, L. Schettino, A.A. Oliveira, C.A. Casotti, R. Pereira, Hyperuricemia is associated with sympathovagal imbalance in older adults, Arch. Gerontol. Geriatr. 90 (2020) 104132, https://doi.org/10.1016/j.archger.2020.104132.
[15] C.J. McMullan, L. Borgi, N. Fisher, G. Curhan, J. Forman, Effect of uric acid lowering on renin-angiotensin-system activation and ambulatory BP: a randomized controlled trial, Clin. J. Am. Soc. Nephrol. 12 (5) (2017) 807–816, https://doi.org/10.2215/CJN.10771016.
[16] P. Palatini, G. Parati, A. Virdis, G. Reboldi, S. Masi, A. Mengozzi, E. Casiglia, V. Tikhonoff, A.F.G. Cicero, A. Ungar, et al., High heart rate amplifies the risk of cardiovascular mortality associated with elevated uric acid, Eur J Prev Cardiol (2021), https://doi.org/10.1093/eurjpc/zwab023.
[17] E.A. Lambert, M. Hachem, R. Hemmes, N.E. Straznicky, N. Eikelis, C.I. Sari, M.P. Schlaich, G.W. Lambert, J.B. Dixon, Serum uric acid and the relationship with subclinical organ damage in adults, J. Hypertens. 35 (4) (2017) 745–752, https://doi.org/10.1097/HJH.0000000000001212.