Research Article

Elevated Serum Uric Acid and Self-Reported Heart Failure in US Adults: 2007–2016 National Health and Nutrition Examination Survey

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Keywords

Cardiovascular disease · Purines · Population data

Abstract

Introduction: There is limited evidence examining the relationship between elevated serum uric acid (sUA) concentration and heart failure (HF) in United States (US) adults. The aim of the present study was to examine the association(s) between elevated sUA and HF using a nationally representative sample of US adults. **Methods:** The final sample with complete data for this analysis ($n = 17,349$) included men and women aged ≥ 40 years who participated in the 2007–2016 National Health and Nutrition Examination Survey. Self-reported diagnosis of HF was assessed via interview. Elevated sUA was defined as values > 6.0 mg/dL for women and > 7.2 mg/dL for men. Multivariable gender-stratified logistic regression was utilized to examine the odds of self-reported HF. **Results:** The estimated prevalence of HF was 3.9 and 3.4% among men and women, respectively. Age-adjusted analysis revealed significantly increased odds of HF in men (OR 2.79; 95% CI 2.15–3.84, $p < 0.01$) and women (OR 3.24; 95% CI 2.37–4.44, $p < 0.01$) with elevated sUA. This relationship remained statistically significant following adjustment for age, race, education, income, alcohol consumption, smoking status, blood pressure, diabetes, physical activity level, cholesterol, creatinine level, and body mass index in men (OR 1.70; 95% CI 1.13–2.57 $p < 0.05$) and women (OR 1.74; 95% CI 1.18–2.58, $p < 0.05$). **Conclusions:** In a representative sample of US adults, having an elevated sUA concentration was associated with significantly increased odds of HF when compared to adults with normal sUA.

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Introduction

Serum uric acid (sUA), or urate, is the end product of purine metabolism that occurs predominately in the liver, muscles, and intestine [1, 2]. Purines can be synthesized in the body, primarily the liver, by de novo synthesis or derived from dietary sources such as purine-rich proteins or fructose [3]. sUA may be elevated for various reasons including excess purine intake, increased enzymatic activity, decreased excretion, or a combination of the 3. In the liver, the rapid phosphorylation of fructose to fructose 1-phosphate decreases intracellular phosphate and adenosine triphosphate [4]. The accumulation of fructose-1 phosphate and depletion of intracellular phosphate stimulates adenosine monophosphate deaminase to catalyze adenosine monophosphate to inosine, a purine nucleoside [5]. Inosine is converted to hypoxanthine, which is oxidized by xanthine oxidase (XO) to form xanthine, and then again by XO to form uric acid. Additionally, increased XO activity in response to several possible factors including hormones, ischemia, and inflammation, may also lead to elevated sUA; however, the mechanistic pathways behind these processes warrant further investigation [2, 6]. Lastly, since 75% of sUA excretion occurs via the kidneys, decreased renal excretion may also result in elevated sUA levels and has been reported as the most common cause of hyperuricemia [3]. Decreased excretion may be due to increased reabsorption at the proximal tubule due to low intravascular volume and sodium concentration of glomerular filtrate, or secretion may be decreased due to angiotensin II. Although investigators have found sUA to have antioxidant properties [7], elevated sUA, or hyperuricemia, has also been associated with an increased risk of several adverse outcomes including metabolic syndrome (MetS) [8, 9], impaired kidney function [9, 10], cardiovascular disease (CVD) mortality [11], and all-cause mortality [12]. Currently, there are no universally accepted cutpoints for hyperuricemia, which may result in inconsistency between studies; however, investigators frequently use largely similar cutpoints, often corresponding to the upper quartile of sUA concentration. According to prevalence estimates from the 2007–2008 National Health and Nutrition Examination Survey (NHANES) [13] 21.2% of men and 21.6% of women in the United States (US) had elevated sUA (>7.0 mg/dL for men, >5.7 mg/dL for women). Using NHANES 1988–1994 and 1999–2002 data, Odden et al. [10] examined the relationship between hyperuricemia (75th percentile of sUA by gender) and CVD mortality. Following the adjustment for potential covariates, participants in the highest quartile were at a near 50% greater risk of CVD mortality compared to participants in the lowest quartile (hazard ratio 1.48; 95% CI 1.13–1.93).

Hyperuricemia is often asymptomatic and indications for initiating treatment are not definitive and often depend on the patient. A recent prospective cohort study [14] followed adults ≥65 years of age without comorbidities at baseline to determine if asymptomatic hyperuricemia (>7.0 mg/dL for men, ≥6.0 mg/dL for women) increased the risk for coronary artery disease events. Following adjustment for potential confounders, elevated sUA was an independent predictor of coronary artery disease events (hazard ratio 1.71, 95% CI 1.26–2.34). In those that are treated, treatment often consists of urate-lowering pharmaceuticals such as XO inhibitors, uricosuric agents, or sodium-glucose cotransporter 2 inhibitors [3]. However, some of these medications are accompanied by rare side effects [15]; therefore, when indications for initiating treatment are not met, dietary habits, obesity, and other risk factor modifications are recommended. Among other risk factor modifications, physical activity (PA) has been shown to play a protective role in decreasing mortality risk in those with hyperuricemia [9], indicating its potential use in the treatment of hyperuricemia.

The role of hyperuricemia in the development and progression of heart failure (HF) has been of recent interest due to its association with disease severity [16, 17] and mortality [17] in this population. The 2018 American Heart Association statistical update on heart disease and stroke statistics [18] reported that the prevalence of HF in adults 20 years of age and

older has increased from 5.7 million between 2009 and 2012 to 6.5 million between 2011 and 2014. At age 40, the lifetime risk of developing HF is 1 in 5 [19]. Desai et al. [20] reported incident HF developed in 26% of those with hyperuricemia (≥ 7.0 mg/dL for men, ≥ 6.0 mg/dL for women) and 21% of those without ($p < 0.001$) after an 8-year follow-up period. With HF being the third leading cause of death attributable to CVD in the US behind CHD and stroke [18], this evidence underscores the importance of further research on sUA's relationship to HF. We hypothesized that elevated sUA would be associated with a greater risk of HF in US adults. The aim of this study was to examine the associations between hyperuricemia and HF using a nationally representative sample of US adults.

Materials and Methods

Study Design and Population

This study used 10 years of data from the 2007–2016 NHANES, a continuous survey conducted by the National Center for Health Statistics (NCHS) [21]. The NHANES is designed to provide national estimates of the health and nutritional status of noninstitutionalized US civilians over the age of 2-months. Of the 50,588 participants in the total sample, 19,344 were at least 40 years of age and provided responses to the interview portion. Following the exclusion of 14 pregnant women and 73 adults with missing responses related to HF, a total of $n = 19,257$ participants were available for further analysis. Of these participants, 90.4% attended a mobile examination center and provided the serum necessary for the measurement of sUA. Twenty participants with sUA values < 2.0 mg/dL were considered hypouricemic [22] and were excluded from the analysis. The final sample for this study consisted of 8,481 male and 8,913 female participants. The testing and examination procedures were approved by the institutional review board of the NCHS and all participants provided informed consent. The use of the NHANES data was approved by the University of North Florida Institutional Review Board.

Uric Acid

The primary independent variable in this study was elevated sUA defined as concentrations > 7.2 mg/dL for men and > 6.0 mg/dL for women [22]. sUA assays were performed on Beckman Coulter UniCel® Dx C 800 Synchron and Dx C 600i Synchron Clinical Systems, which uses a colorimetric timed endpoint method to obtain quantitative sUA concentrations [21].

Heart Failure

The dependent variable in this study was self-reported HF and was obtained from the NHANES medical conditions files [21]. The questions on HF were administered in the home by an interviewer using the Computer-Assisted Personal Interviewing system as part of the survey participant household interview. The final sample provided yes/no responses to the following question: "Has a doctor or other health professional ever told {you/SP} that {you/s/he}... had congestive HF?"

Other Covariates

Five categories of self-reported race were created: non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, and other. Education status included 4 categories: $<$ high school, high school graduate/General Education Development or equivalent, some college or Associate in Arts degree, and college graduate or above. Income included 5 categories: USD $\leq 14,999$, USD 15,000–34,999, USD 35,000–64,999, USD 65,000–99,999, and USD $\geq 100,000$. Three smoking status categories were created using self-reported history of cigarette use; former smoker, current smoker, and never smoked. Adults who answered "no" to having at least 12 drinks in their lifetime were considered never drinkers. Men who reported 1–2 drink(s)/day and women who reported 1 drink/day were categorized as moderate drinkers. Those who reported more than moderate for their gender were considered above-moderate drinkers. PA participation was dichotomized (yes/no) for any volume of moderate and/or vigorous intensity recreational activities. Diabetes and cholesterol variables were also self-reported and dichotomized (yes/no). Serum creatinine concentrations > 1.18 mg/dL for men or > 1.02 mg/dL for women were considered elevated [21]. The second and third of 3 consecutive blood pressure (BP) measurements were averaged and 3 categories were created using the 2017 American Heart Association BP recommendations [23]. For this analysis, systolic BP (SBP) < 120 mm Hg and diastolic BP (DBP) < 80 mm Hg were considered normal, SBP 120–129 mm Hg and DBP < 80 mm Hg elevated, and SBP ≥ 130 mm Hg or DBP

Table 1. Sample characteristics according to gender and HF status: 2007–2016 NHANES

	HF				No HF			
	<i>n</i>	men Wt. % (SE)	<i>n</i>	women Wt. % (SE)	<i>n</i>	men Wt. % (SE)	<i>n</i>	women Wt.% (SE)
Total	457	50.8 (2.27)	365	49.2 (2.27)	8,024	47.5 (0.54)	8,548	52.5 (0.54)
Age, years, median	69		71		55		56	
Race								
nH white	251	72.2 (2.46)	117	70.2 (2.53)	3,600	73.0 (0.55)	3,716	72.0 (0.52)
nH black	100	12.7 (1.44)	100	16.2 (1.75)	1,627	9.0 (0.26)	1,720	10.4 (0.28)
Mexican American	44	5.01 (0.89)	33	4.3 (0.89)	1,172	6.8 (0.24)	1,275	6.2 (0.20)
Other Hispanic	39	3.96 (0.74)	39	4.5 (0.84)	801	4.5 (0.19)	1,003	4.7 (0.17)
Other	23	6.18 (1.82)	16	4.7 (1.36)	824	6.8 (0.33)	834	6.7 (0.31)
Education								
<High school	161	28.2 (2.55)	140	29.7 (2.86)	2,271	17.4 (0.49)	2,346	17.1 (0.45)
High school graduate	109	25.6 (2.78)	100	29.6 (2.93)	1,848	22.7 (0.66)	1,893	22.3 (0.60)
Some college	125	27.4 (2.84)	93	30.5 (2.28)	1,951	27.6 (0.71)	2,439	31.3 (0.69)
≥ College graduate	61	18.8 (2.66)	31	10.2 (2.09)	1,950	32.2 (0.76)	1,857	29.2 (0.71)
Income								
USD ≤14,999	93	14.5 (1.71)	91	22.7 (2.71)	928	6.7 (0.30)	1,285	10.3 (0.36)
USD 15,000–34,999	159	35.5 (3.06)	133	43.2 (3.49)	1,956	18.4 (0.55)	2,219	22.3 (0.57)
USD 35,000–64,999	96	28.5 (3.18)	65	20.6 (2.85)	1,790	24.0 (0.69)	1,868	25.0 (0.67)
USD 65,000–99,999	45	13.4 (2.48)	28	10.2 (2.26)	1,116	19.7 (0.69)	1,041	16.8 (0.61)
USD ≥100,000	22	8.2 (1.98)	9	3.3 (1.33)	1,431	30.9 (0.82)	1,249	25.5 (0.75)
BMI, kg/m ²								
Underweight	21	4.3 (1.25)	25	6.4 (1.42)	203	2.0 (0.20)	223	2.59 (0.23)
Normal	82	15.0 (2.03)	63	18.6 (2.67)	1,841	20.6 (0.62)	2,137	28.5 (0.68)
Overweight	135	31.7 (2.89)	81	19.6 (2.39)	3,242	41.1 (0.77)	2,558	30.1 (0.67)
Obese	219	49.0 (3.12)	196	55.4 (3.26)	2,738	36.4 (0.76)	3,630	38.8 (0.70)
WC								
Healthy	193	36.9 (2.88)	121	32.8 (3.03)	4,258	49.5 (0.78)	2,512	31.6 (0.69)
At risk	264	63.1 (2.88)	244	67.2 (3.03)	3,766	50.5 (0.78)	6,036	68.4 (0.69)
Blood pressure								
Normal	60	16.7 (2.60)	33	9.4 (1.94)	2,069	28.7 (0.72)	2,602	33.9 (0.71)
Elevated	24	5.4 (1.30)	9	2.0 (0.70)	899	12.3 (0.53)	834	10.8 (0.48)
Hypertensive	373	77.8 (2.76)	323	88.6 (2.05)	5,056	59.1 (0.78)	5,112	55.3 (0.73)
Physical activity								
Yes	17	4.0 (1.12)	6	3.1 (1.46)	927	15.0 (0.60)	695	11.3 (0.51)
No	440	96.0 (1.12)	359	96.9 (1.46)	7,097	85.0 (0.60)	7,853	88.7 (0.51)
Alcohol								
Never	31	10.0 (2.07)	97	39.5 (4.13)	583	7.9 (0.46)	1,804	20.0 (0.60)
Moderate	150	63.6 (3.79)	69	39.7 (4.33)	3,033	56.8 (0.91)	2,341	42.5 (0.86)
Above moderate	251	26.4 (3.53)	47	20.8 (3.56)	2,067	35.2 (0.88)	2,028	37.5 (0.85)
Smoking status								
Current smoker	134	21.3 (2.57)	199	15.8 (2.49)	3,357	19.8 (0.61)	5,347	15.8 (0.53)
Former smoker	223	51.0 (3.11)	108	32.8 (3.20)	2,932	34.9 (0.74)	1,886	24.9 (0.65)
Never smoked	99	27.7 (2.68)	58	51.4 (3.32)	1,726	45.3 (0.78)	1,308	59.3 (0.72)
Family history of CVD								
Yes	102	23.0 (2.74)	93	31.6 (3.40)	860	12.2 (0.52)	1,221	15.6 (0.54)
No	334	77.0 (2.74)	252	68.4 (3.40)	6,938	87.8 (0.52)	7,123	84.4 (0.54)
Diabetes								
Yes	175	35.5 (3.03)	161	45.2 (3.38)	1,442	14.6 (0.52)	1,354	11.7 (0.42)
No	264	64.5 (3.03)	190	54.8 (3.38)	6,330	85.4 (0.52)	6,948	88.3 (0.42)
Uric acid, mg/dL								
Normal	297	66.1 (2.98)	183	50.5 (3.32)	6,722	84.8 (0.55)	6,863	82.0 (0.54)
Elevated	160	34.0 (2.98)	182	49.5 (3.32)	1,302	15.2 (0.55)	1,685	18.0 (0.54)
Creatinine, mg/dL								
Mean (SE)		1.25 (0.04)		1.11 (0.03)		1.01 (0.01)		0.80 (0.01)
eGFR, mL/min/1.73 m ²								
Mean (SE)		69.48 (1.38)		63.62 (1.59)		86.12 (0.25)		85.59 (0.26)

Uric acid, mg/dL (elevated >7.2 for men and >6.0 for women). BMI, kg/m² (underweight <18.5, normal weight 18.5–24.9, overweight 25.0–29.9, and obese ≥30.0). WC, cm (at risk >102 for men or >88 for women). Creatinine, mg/dL (elevated >1.18 for men or >1.02 for women). BP, mm Hg (normal: SBP <120 and DBP <80, elevated: SBP 120–129 and DBP <80 elevated, hypertensive SBP ≥130 or DBP ≥80).

HF, heart failure; NHANES, National Health and Nutrition Examination Survey; Wt., weighted; BMI, body mass index; nH, non-Hispanic; WC, waist circumference; CVD, cardiovascular disease. eGFR, estimated glomerular filtration rate; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. ORs for self-reported HF in US adults with hyperuricemia compared with their normouricemic counterparts: NHANES 2007–2016

Model	Men			Women		
	OR	95% CI	p value	OR	95% CI	p value
Unadjusted	2.87	2.15–3.84	<0.001	4.46	3.29–6.04	<0.001
Age-Adjusted	2.79	2.08–3.73	<0.001	3.24	2.37–4.44	<0.001
Fully-Adjusted(a)	1.70	1.12–2.59	0.019	1.74	1.18–2.58	<0.01
Fully-Adjusted(b)	1.69	1.11–2.57	0.021	1.86	1.25–2.78	<0.001

Hyperuricemia >7.2 mg/dL for men and >6.0 mg/dL for women. Fully-Adjusted(a) for age, education, income, race, BMI, alcohol consumption, smoking status, BP, physical activity, diabetes, cholesterol, and creatinine. Fully-Adjusted(b); Fully-Adjusted(a) plus WC in place of BMI.

NHANES, National Health and Nutrition Examination Survey; HF, heart failure; BMI, body mass index; BP, blood pressure; WC, waist circumference.

≥80 mm Hg hypertensive. Participants who reported antihypertensive medication use were also considered hypertensive, as this would carry the diagnosis. Four categories of body mass index (BMI) [24] were created; <18.5 kg/m² were classified as underweight, 18.5–24.9 kg/m² normal weight, 25.0–29.9 kg/m² overweight, and ≥30.0 kg/m² obese. Waist circumference (WC) was dichotomized as at risk or healthy. Values ≥102 or ≥88 cm for men and women, respectively, were considered at risk [25]. Family history of CVD [21] included yes/no responses to the following question: “Including living an deceased, were any of {SP’s/your} close biological that is, blood relatives including father, mother, sisters, or brothers, ever told by a health professional that they had a heart attack or angina (an-gi-na) before the age of 50?” Estimated glomerular filtration rate was analyzed using the Chronic Kidney Disease Epidemiology Collaboration equation [26].

Statistical Analysis

The data in this study were managed using SAS version 9.4 (SAS Institute, Cary, NC, USA) [27]. SAS was used for data recoding, data coding validation, and data analysis. Sampling weights within the context of the correlated multistage complex sampling design inherent to the NHANES were used. Gender-stratified models were used for the statistical analyses as recent evidence [28] has found an interaction between gender and sUA on all-cause mortality in HF patients. Additionally, an interaction test was used to evaluate the effects of gender and sUA in relation to HF in this analysis. Logistic regression analyses were used to examine the odds of self-reported HF by hyperuricemia. The fully adjusted gender-stratified best-fit model included age, race, education, income, alcohol consumption, smoking status, BP, diabetes, PA level, cholesterol, creatinine level, and either BMI or WC. Separate models were used when including BMI or WC due to the collinearity of these 2 variables. Additionally, gender-stratified logistic regression analysis was also used to estimate the adjusted odds of HF by quartiles of sUA. The level of significance was set at $\alpha = 0.05$ for all tests.

Results

Elevated sUA and HF Prevalence and Risk

Table 1 illustrates sample characteristics according to gender and HF status.

Among adult males and females, the age-adjusted prevalence of elevated sUA in the total sample was 15.9 and 19.1% respectively. The prevalence of HF in the total sample was 3.6% (3.9% of men and 3.4% of women, $p = 0.14$). Of participants with HF, 34.0% of men and 49.5% of women ($p < 0.01$) had hyperuricemia, while only 15.2% of men and 18.0% of women ($p < 0.001$) without HF had hyperuricemia. Table 2 shows the OR of self-reported HF in participants with hyperuricemia.

Fig. 1. Adjusted ORs of self-reported HF in adult males with elevated sUA concentrations, 2007–2016 NHANES. Adjusted for age, race, education, income, alcohol consumption, smoking, BP, diabetes, PA level, cholesterol, creatinine level, and BMI. Error bars represent 95% CIs. sUA, serum uric acid.

Fig. 2. Adjusted ORs of self-reported HF in adult females with elevated sUA concentrations, 2007–2016 NHANES. Adjusted for age, race, education, income, alcohol consumption, smoking, BP, diabetes, PA level, cholesterol, creatinine level, and BMI. Error bars represent 95% CIs. sUA, serum uric acid.

Interaction test revealed a significant ($p < 0.05$) interaction between gender and sUA in relation to HF. In the age-adjusted model, men with hyperuricemia were almost 3 times more likely to report being diagnosed with HF compared to those with normal concentrations (OR 2.79; 95% CI 2.09–3.71). Age-adjusted OR of women with hyperuricemia was even higher at 3.24 (95% CI 2.37–4.44). In the fully adjusted model, OR for men and women were attenuated but remained statistically significant (OR 1.70; 95% CI 1.13–2.57 and 1.74; 95% CI 1.18–2.58 respectively). When BMI was replaced with WC, ORs were 1.69 (95% CI 1.12–2.55) for men and 1.86 (95% CI 1.25–2.78) for women, remaining significant.

Figures 1 and 2 illustrate the fully adjusted OR of self-reported HF by quartiles of sUA concentration for adult males and females respectively. Both males and females in the upper quartile of sUA were significantly more likely to report HF compared to those in the lowest quartile. An illustration of the fully adjusted OR of self-reported HF by quartiles of sUA for the total sample size can be found in the online (www.karger.com/doi/10.1159/000502438) supplementary materials.

Discussion

Whether sUA is elevated secondary to overproduction, underexcretion, or both, is unclear. In our sample, one third of males and about half of females with HF had hyperuricemia. The prevalence of hyperuricemia was significantly higher in women compared to that in men inde-

pendent of the HF status. Hyperuricemia was shown to be positively associated with risk of HF in both genders. These findings are consistent with previous research [16, 17] showing significant associations between hyperuricemia and HF following adjustment for several covariates. Similar to the 2014 study by Odden et al. [10] in which participants in the highest quartile of sUA had a significantly increased risk of CVD mortality, there was a significant association between the highest quartile of sUA and HF in our analysis for both males and females. Compared to Zhu et al. [13] 2007–2008 NHANES prevalence estimates of hyperuricemia in adults without HF (21.2% for men and 21.6% for women), estimates in this analysis were lower at 15.9% for men and 19.1% for women. This difference is likely because the prior study included adults ≥ 20 years of age, whereas this analysis only included adults ≥ 40 years of age.

Gender differences in the prevalence of sUA seen in our analyses have been previously reported [14, 16, 22] and is commonly reported in studies including samples of older adults and postmenopausal women. A prospective cohort study [9] reported a decrease from 7.0 to 6.7 mg/dL in mean sUA levels in males from age 20 to 80 but an increase in mean sUA from 5.0 to 6.2 mg/dL after the age of 45 in females. This increase in sUA level after menopause is consistent with other investigations and has been attributed to the impact of decreased estrogens after menopause. Using data on 7,662 women from the NHANES III, Hak et al. [29] reported that sUA levels did not vary significantly between age groups until the 40–49 years category and increased with each age category thereafter ($p < 0.001$). However, after adjusting for estimated glomerular filtration rate in one model and creatinine levels, diuretic use, and hypertension in another model, the trend was no longer significant for either of the models. Postmenopausal hormone use was associated with lower uric acid levels independent of other risk factors. This evidence suggests that the increase in sUA after menopause is likely due to the impact of decreased estrogens on renal tubular uric acid excretion.

Other hormones aside from estrogens may also help explain the increase in sUA concentration in some adults. In a 2013 review paper, Li et al. [8] examined the relationship between MetS, type 2 diabetes, and hyperuricemia, and proposed hyperinsulinemia as a possible mediating factor between hyperuricemia and MetS. They reported potential causal effects of hyperuricemia and insulin resistance on each other. On the one hand, hyperuricemia has been shown to impair endothelial function primarily through the inhibition of nitric oxide bioavailability, which can induce insulin resistance. On the other hand, hyperinsulinemia may decrease uric acid clearance in the kidneys due to the effects of hyperinsulinemia on proximal tubular urate transport.

One possible explanation for the association between sUA concentrations and HF in this population is the greater use of diuretics [17]. Diuretics can cause elevated sUA levels, which could be a mediator between hyperuricemia and HF. This would indicate that sUA is not a causative factor and is more likely elevated secondary to diuretics use in the treatment of HF. However, this is not settled science, evidence [30] exists supporting the association between hyperuricemia and HF independent of diuretic use as well.

Though not a form of urate-lowering therapy, Chen et al. [9] reported PA may play a similar role in decreasing mortality risk in hyperuricemic adults. Participants that reported being “fully active” (30 min/day for at least 5 days/week) had a mortality risk reduction equivalent to a 3.4 mg/dL decrease in sUA concentration. This amount of PA shown to reduce mortality risk in this population meets the updated 2018 PA Guidelines for Americans by the Department of Health and Human Services [31]. Additionally, in a recent review on the health benefits of exercise, Rueggsegger and Booth [32], addressed the strong association between cardiorespiratory fitness, chronic disease, and mortality and highlights the role of exercise in delaying the onset of 40 chronic conditions/diseases. Considering these implications, hyperuricemic patients should be encouraged to engage in, at minimum, sufficient PA to meet these guidelines.

Despite the growing body of literature examining the relationship between hyperuricemia and CVD, the conclusions are ambiguous and there is not a clear mechanistic explanation for this association. There are also no accepted standardized hyperuricemia cutpoints, which may account for some of the variance between studies. The different cutpoints seen throughout the literature could result in nonsignificant findings when there may indeed be an association. This also makes it difficult to directly compare studies due to the lack of consistency.

This study is not without limitations; inherent to the cross-sectional design, a temporal relationship between sUA and HF cannot be determined therefore, we are unable to confirm whether this relationship is causal. Moreover, the use of self-reported HF as the primary outcome variable can increase the possibility for misclassification because it is subject to recall bias. sUA can be acutely elevated for various reasons, such as acute exercise [7], and because the data used in this study were collected at a single time-point, it is unknown if sUA was acutely, and not chronically, elevated. A strength of this study is the use of a large nationally representative sample of US adults. This is important because it increases the external validity of our findings, which is a limitation in smaller HF studies that may not have been adequately powered to examine these associations.

The results of this study suggest that hyperuricemia was significantly associated with greater odds of self-reported HF in men and women, independent of several potential confounders. Future investigation is necessary to determine the mechanisms by which sUA and HF are associated. With further evidence, clinicians may consider the use of PA in combination with urate-lowering therapies to decrease mortality risk in this population. There should be a focus on establishing a harmonious quantitative definition of hyperuricemia in order to produce more consistent and comparable evidence and to aid clinicians in determining when to diagnose and treat asymptomatic hyperuricemia.

Statement of Ethics

The testing and examination procedures were approved by the Institutional Review Board of the NCHS and all participants provided informed consent. The use of the NHANES data was approved by the University of North Florida Institutional Review Board.

Disclosure Statement

No conflict of interest applies for any of the authors regarding this study. No funding or grant were used or obtained for this study.

Author Contributions

M.L.S.: designed the study, contributed the statistical analysis, and served as the primary author of the manuscript. Mr. Michael R. Richardson and Dr. James R. Churilla contributed to the statistical analysis and assisted with the study design and the writing of the manuscript. Mr. Larry Guevara along with Ms. Bethany G. Rand contributed to the statistical analysis and assisted with the writing of the manuscript and served as editors.

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