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A U-Shape Association of Serum Uric Acid with Gout in US Adults

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Abstract

Background: Serum uric acid (SUA) level is the strongest determinant of gout, and the relationship between hyperuricemia and gout has been found. However, the association between the across-full range of SUA level and gout also remains uncertain. We aimed to investigate the trend across an across-full range of SUA level and gout in the general population.

Method: This study included 4,846 US adults from the National Health and Nutrition Examination Survey (NHANES). A generalized additive model (GAM) was used to fit the non-linear trend between SUA level and gout. Risk factors associated with gout and general factors were included in the models as covariates. The subgroup analyses were conducted by gender and age.

Results: 2,326 males and 2,520 females were included in our study. The prevalence of gout was 5.67%. The results of multivariable GAM showed a U-shape association between SUA level and gout (EDF = 4.280, p <0.001). The subgroup analyses showed a positive U-shape trend in male with the lowest point of 5.5 mg/dL (EDF = 4.471, p <0.001), while a linear shape in female (EDF = 1.001, p =0.354). And we found that a U-shape trend between SUA level and gout with a turning point at 5.5 mg/dL in 20-54 years and over 65 years participants in male while a linear shape in different age group in female.

Conclusion: This study showed that not only high SUA level was associated with gout, but also low SUA level. Hypouricemia is a candidate predictor of gout in US adult males.

Keywords: Gout; U-shape; Hyperuricemia; Hypouricemia; generalized additive model

Introduction

Gout is a clinical syndrome characterized by elevated blood uric acid levels caused by purine metabolism disorders, deposition of monosodium urate crystals, and tissue damage [1]. According to the Global Burden of Disease (GBD) 2017, there were 41.2 million (95% *UI*: 36.7 million~46.1 million) adults with gout worldwide. In 2017, the age standardized point prevalence estimate and the increase of age-standardized point prevalence estimate of gout in the United States ranked among the top three in the world [2]. A prospective cohort study showed that the all-cause standardized mortality in gout patients was 2.21 (95% *CI*: 1.68-2.74) [3]. In addition, gout is associated with several diseases, including joint pain, chronic kidney disease (CKD), hypertension, type 2 diabetes, dyslipidemia, etc [4], which has effect on the life [5], productivity [6,7] and health-related quality of life (HRQOL) [8,9]. High uric acid (hyperuricemia) is the strongest determinant of gout, and many studies have proved the existence of this association [10-12]. SUA level can be maintained at a certain target level through urate-lowering treatment (ULT), effectively reducing the incidence of gout [13, 14]. Although some researches on high SUA level and gout have been reported, the underlying association between across-full range of SUA level and gout is still uncertain.

There is currently a lack of consensus regarding the optimal range for SUA level. Previous studies focus on the relationship between high uric acid and gout. An analysis using Cox proportional hazards model in a cohort study in Japan showed that in subjects with asymptomatic hyperuricemia, controlling SUA level can reduce or eliminate gout occurrences [15]. In another Mendelian randomization study, it presented convincing evidence that the increased risk of gout was associated with high SUA level (n=71 501, *OR*: 5.84; 95% *CI*: 4.56-7.49, p<0.01) [16]. However, few studies have evaluated the prevalence of gout across the full range of SUA level in adults.

Previous studies have shown U-shaped associations between SUA levels and cardiovascular mortality [17], kidney disease [18, 19], and all-cause mortality [20]. D'silva et al reported that the risk of all-cause mortality risk among US males with SUA level <4 mg/dL was about 30% higher [21], which indicates that both hyperuricemia and hypouricemia are risk factors to human health. However, the risk of gout development in patients with hypouricemia has not yet been clarified. Gout and chronic kidney disease frequently coexist [22] which potentially indicate that the relationship between low SUA level and gout also needs to be further clarified.

Therefore, based on the National Health and Nutrition Examination Survey (NHANES), we explore the trend between SUA level and gout by gender and age.

Materials and Methods

Data Source and Study Population

The National Health and Nutrition Examination Survey (NHANES) is a unique source of national data on the health and nutritional status of the US population, collecting data through interviews, standard exams, and biospecimen collection. NHANES adopts a stratified and multi-stage sampling design, and the survey population involves each county in US. Each year, about 5,000 persons in 15 counties are selected to conduct a nationally representative sample survey. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. Health interviews are conducted in respondents' homes. Health measurements are performed in specially-designed and equipped mobile centers, which travel to locations throughout the country. The study team consists of a physician, medical and health technicians, as well as dietary and health interviewers. All procedures were approved by the NCHS Research Ethics Review Board (Continuation of Protocol #2011-17 http://www.cdc.gov/ nchs/nhanes/irba98.htm), and all participants provided written informed consent.

For our study, we used the publicly available files for the NHANES 2017-2018 cycles. We included adults (ages 20 years and older) who had uric acid data and gout data

(n=4,908). Participants were excluded if they were prescribed ULT (taken prescription medicine allopurinol in the past month) during the period (n=26). Participants who refuse to answer or answer "I don't know" in covariates variables (age, education, marital status, diabetes, kidney disease, hypertension, smoke, alcohol) were also excluded (n=36). Eventually, 4,846 participants were included in our study. The flow chart of participant inclusion and exclusion is shown in Figure 1 and the distributions of the number of participants with different value of uric acid are shown in Figure 2.

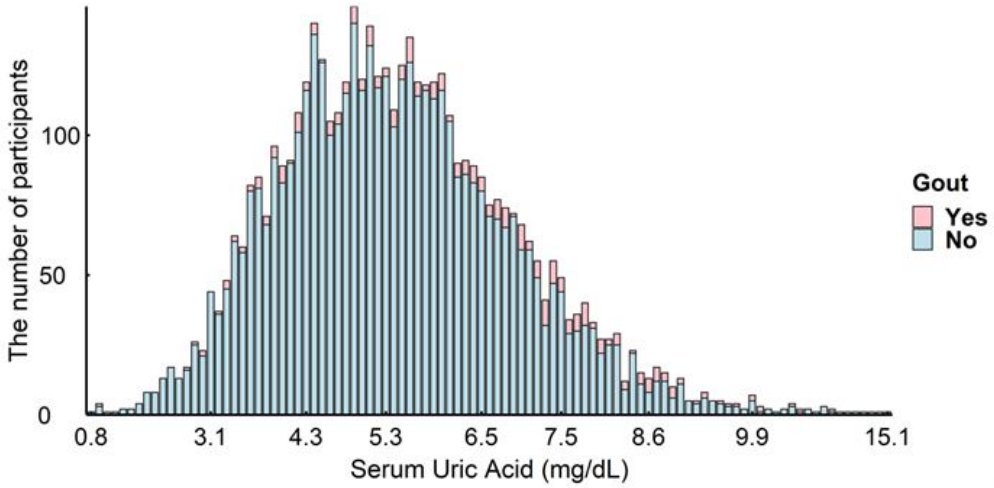

Image1: Flow chart of participant inclusion and exclusion.

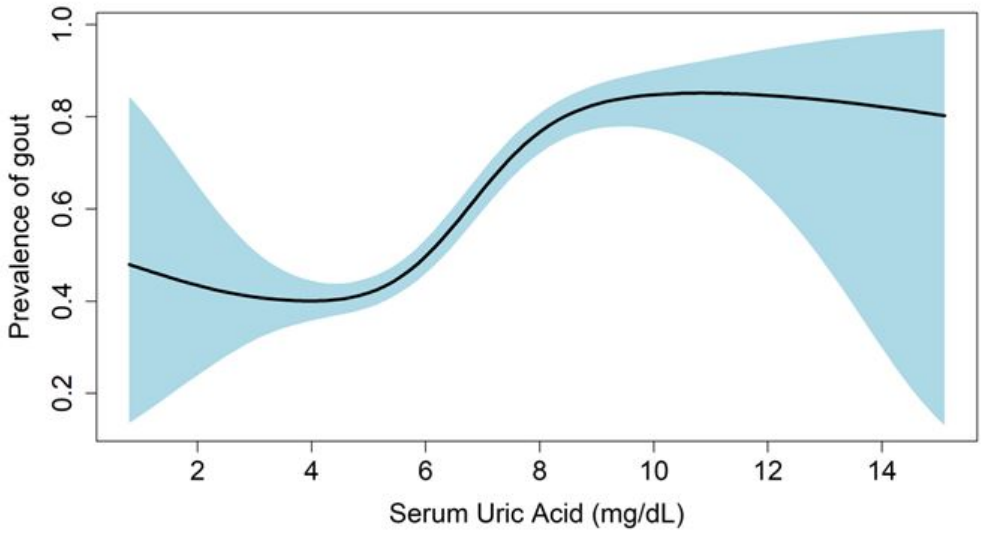

Image2: Distribution of the number of participants with different value of uric acid.

Variable Measurements

Socio-demographic factors and modifiable risk factor of gout were included in this study. We obtained the data of these variables from seven parts of following: "Demographic Data", "Standard Biochemistry Profile", "Alcohol Use", "Blood Pressure & Cholesterol", "Smoking - Cigarette Use", "Kidney Conditions - Urology" and "Medical Conditions".

Gout

Gout was self-reported data. Whether participants have gout was defined using the question, “Has a doctor or other health professional ever told you that you had gout?”.

Serum Uric Acid Level

In this study, we used the SUA level in the laboratory data as interested independent variable and recorded as a continuous variable. The detail process of laboratory data measurement was described in the NHANES database official website. (https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/BIOPRO_J.htm)

Covariates

The covariates included gender, age, education, marriage, race, alcohol drinking, smoking, hypertension, diabetes and kidney disease. Age was divided into three groups: 20-54, 55~64, and over 65 years. Education level was categorized into primary and secondary, high school, above high school. Marriage was grouped into three categories: married or living with a partner, widowed divorced or separated, never married. Race was divided into five categories: Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race - including Multi-Racial. Alcohol drinking was classified as never drink, light drinking, moderate drinking, and heavy drinking, which was defined as 0, < 1, 1- < 4, and >4 drinks per week. Smoking was defined as "at least 100 cigarettes in a lifetime". Diagnosis of hypertension, diabetes and kidney disease were determined with questions: "Have you ever been told by a doctor or health care provider that you have high blood pressure, diabetes or problems with high blood sugar, weak or failing kidneys".

Statistical Analysis

Descriptive statistics on participants’ characteristics were stratified by whether they had gout. Chi-squared test was utilized to determine the association between categorical variables. The GAM was used to assess the potential association between SUA level and gout. The GAM approach is an extension of the generalized linear model (GLM) with a linear predictor involving a sum of smooth functions of covariates. The smoothness of the model terms was estimated as part of fitting using penalized cubic regression splines, “EDF=1” means a linear pattern of the relationship, “EDF >1” means a non-linear relationship. The models with lower difference between EDF and reference degree of freedom (Ref.df) were commonly considered to be better-fitting models. As the response variable (gout) in this study was a categorical one, we chose “Logit” as our link function, and the effects were estimated by restrictive maximum likelihood (REML) [23].

In our analysis, we fit three GAM models to NHANES data. The three models used gout (yes/no) as a binary response. Model 1 used a smoothing spline function of SUA level as the nonparametric part and covariates were included linearly as the parametric part. Model 2 was similar to model 1 but the subgroup analyses conducted by gender was added to the model. Model 3 adds age subgroup analysis on the basis of model 2.

SAS 9.4 (Statistical analysis system) was used for data cleaning and statistical description. GAM in our analysis was using the "mgcv" package in R statistical software (version 4.1.1). The statistical tests were two-sided, and the significance level was set at 0.05.

Results

Characteristics of Participants

A total of 4,846 eligible participants (2,326 males and 2,520 females) were included in our study, with the age range of 20~80 years. About 52.00% were female, and 56.40% educated in above high school. About 5.67% of participants had gout. All factors had significant statistical differences except education, details are shown in Table 1.

Table1: characteristics of the participants according to gout

	n (%)	Gout		*P*
		Yes(*n*=275)	No(*n*=4571)	
Uric Acid(mg/dL)		6.34±1.79	5.41±1.45	<0.001**
Gender				
Male	2326(48.00)	189(8.13)	2137(91.87)	<0.001**
Female	2520(52.00)	86(3.41)	2434(96.59)	
Age				
20-54 years	2564(52.90)	63(2.45)	2501(97.55)	<0.001**
55-64 years	1027(21.19)	72(7.01)	955(92.99)	
Over 65 years	1255(25.89)	140(11.15)	1115(88.85)	
Education				
Primary and secondary	404(8.34)	20(4.95)	384(95.05)	0.694
High	1709(35.27)	94(5.50)	1615(94.50)	
Above high	2733(56.40)	161(5.89)	2572(94.11)	
Race				
Mexican American	670(13.83)	24(3.58)	646(96.42)	0.011*
Other Hispanic	455(9.39)	16(3.52)	439(96.48)	
Non-Hispanic White	1695(34.98)	112(6.61)	1583(93.39)	
Non-Hispanic Black	1100(22.70)	64(5.82)	1036(94.18)	
Other Race - Including Multi-Racial	926(19.11)	59(6.37)	867(93.63)	
Marital Status				
Married or living with partner	2860(59.02)	167(5.84)	2693(94.16)	<0.001**
Widowed、Divorced or Separated	1118(23.07)	84(7.51)	1034(92.49)	
Never married	868(17.91)	24(2.76)	844(97.24)	
Smoking				
Yes	2034(41.97)	159(7.82)	1875(92.18)	<0.001**
No	2812(58.03)	116(4.13)	2696(95.87)	
Alcohol				
Never drink	958(23.44)	71(7.41)	887(92.59)	0.001*
Light drinking	2301(56.30)	104(4.52)	2197(95.48)	
Moderate drinking	550(13.46)	33(6.00)	517(94.00)	
Heavy drinking	278(6.80)	24(8.63)	254(91.37)	

Kidney disease				
Yes	196(4.04)	40(20.41)	156(79.59)	<0.001**
No	4650(95.96)	235(5.05)	4415(94.95)	
Diabetes				
Yes	769(15.87)	103(13.39)	666(86.61)	<0.001**
No	3922(80.93)	159(4.05)	3763(95.95)	
Borderline	155(3.20)	13(8.39)	142(91.61)	
Hypertension				
Yes	1842(38.01)	178(9.66)	1664(90.34)	<0.001**
No	3004(61.99)	97(3.23)	2907(96.77)	

Model 1: Gout and Serum Uric Acid

Model 1 used gout (Yes/No) as a binary response and adjusted for covariates. A non-linear shape was found between SUA level and gout (*EDF*=4.280, $p<0.001$), and the predicted smooth association of SUA level and gout including the 95% confidence intervals, was shown in Figure 3. The figure showed a U-shape association of SUA level and the prevalence of gout in multivariable GAM models. The lowest prevalence observed was SUA level of 5.0-6.0mg/dL. SUA level had the strongest effect on gout at the SUA level which was at 3.0-10.0 mg/dL. While SUA level exceed 11.0 mg/dL, the prevalence of gout began to decline slowly. The results of non-linear parameters of GAM were presented in Table 2, the parameter section results were detailed in supplementary table S1.

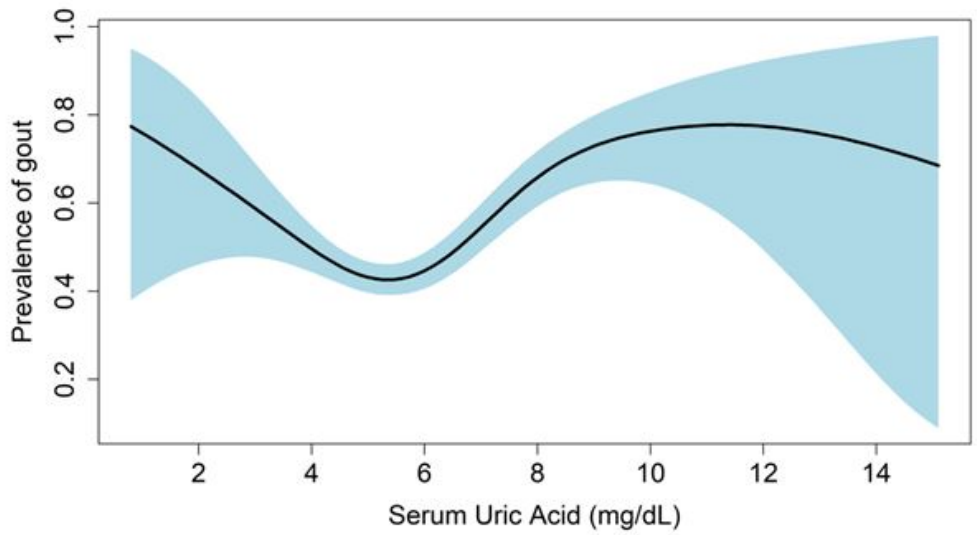

Image3: Figure of estimated smoothing spline function of prevalence of gout (The reference group is participants without gout) with 95% confidence band for the multivariable generalized additive model 1 adjusted for gender, age, marital status, education, race, smoking, alcohol, diabetes, kidney disease and hypertension.

Table2: The smooth function of gout measured by the GAM (model1)

Smooth terms	EDF	Ref.df	X2	P
Reference (Yes)				
Gout (No)	4.28	5.327	46.29	<0.001

Model 2: Gout and Serum Uric Acid (Group by Gender)

Furthermore, the subgroup analyses were conducted by gender in order to further explore the relationship between SUA level and gout in male and female and was evaluated in model 2.

The significant result indicates a non-linear shape between SUA level and gout in male (*EDF*=4.471, $p<0.001$, see Figure4a), which was similar to the trend of entire participants. There are two turning points, which were 5.5 mg/dL and 11.0 mg/dL. The lowest risk of gout is observed at SUA level 5-6mg/dL. Extreme low SUA level or SUA level at 6.0-10.0 mg/dL will increase the risk.

However, the non-linear shape between SUA level and gout was not significant statistically in female (*EDF*=1.001, $p=0.309$, see Figure4b). The risk of gout increased linearly with the increase of SUA level. The results of non-linear parameters of GAM were presented in Table 3, the parameter section results were detailed in Table S2.

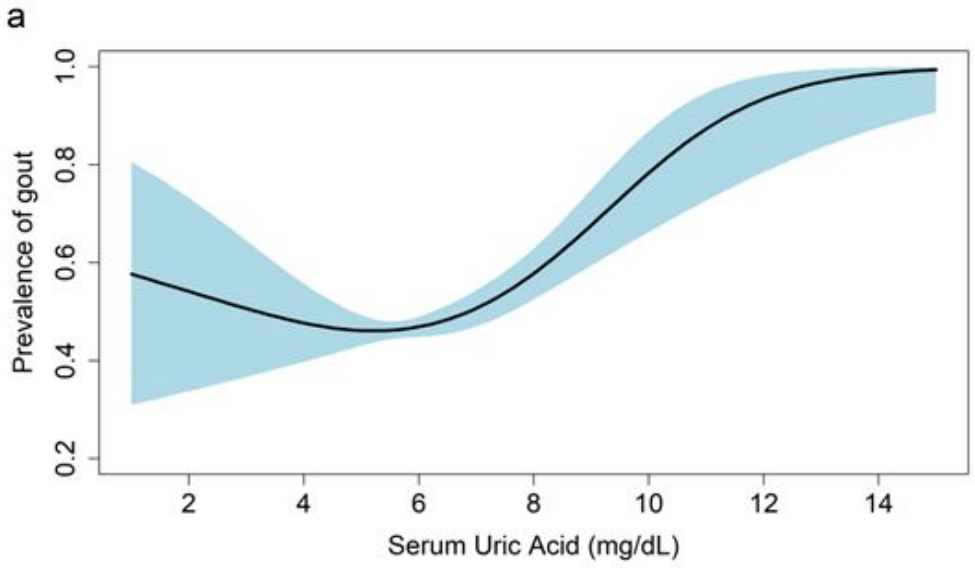

Image4: Figures of estimated smoothing spline function of prevalence of gout level (Group by gender, and the reference group is participants without gout) with 95% confidence band for the multivariable generalized additive model 2. And a for male, b for female.

Table3: The smooth function of gout measured by the GAM (Group by gender) (model2)

Smooth terms	EDF	Ref.df	X2	P
Reference (Yes)				
Spline (Uric Acid): Male	4.471	5.562	53.12	<0.001

Spline (Uric Acid): Female	1.001	1.002	0.862	0.354

Model 3: Gout and Serum Uric Acid (Group by Age in Male and Female)

In addition, we also evaluated the relationship between SUA level and gout in different age groups in male and female. The results revealed that different non-linear trends were found for 20-54years participants in male (*EDF*=3.352, $p<0.001$, see Figure5a), 55-64 years participants in male (*EDF*=1.795, $p=0.002$, see Figure5c), over 65 years participants in male (*EDF*=4.498, $p<0.001$, see Figure5e), 20-54years participants in female (*EDF*=1.000, $p=1.801$, see Figure5b), 55-64 years participants in female (*EDF*=1.000, $p=393$, see Figure5d) and over 65 years participants in female (*EDF*=1.000, $p=0.477$, see Figure5f).

The result showed a U-shape trend between SUA level and gout with a turning point at 5.5 mg/dL in 20-54 years and over 65 years participants in male. Meanwhile, a linear trend was found in different age group in female. The results of non-linear parameters of GAM were presented in Table 4, the parameter section results were detailed in Table S3.1 for male and Table S3.2 for female.

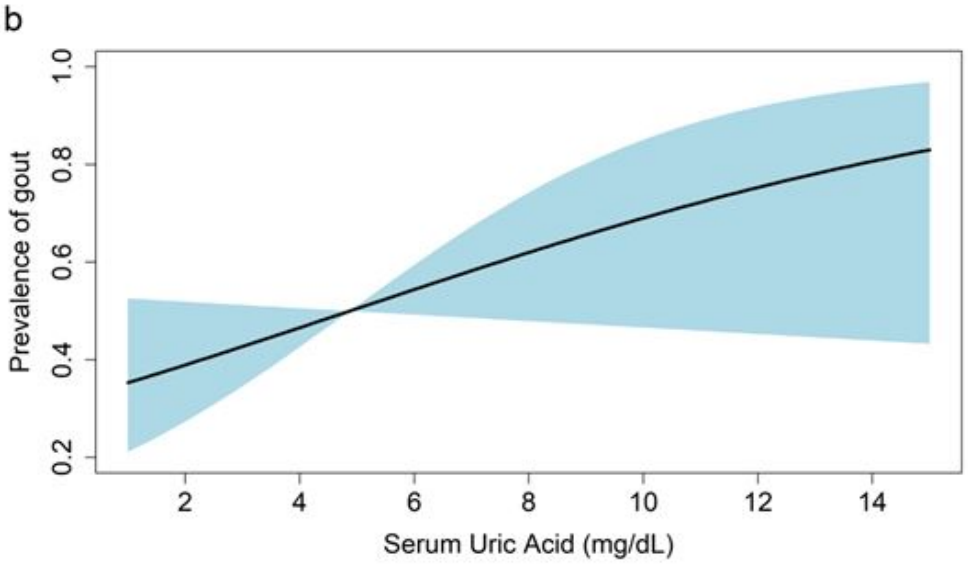

Image5: Figures of estimated smoothing spline function of prevalence of gout level (Group by age in male and female, and the reference group is participants without gout) with 95% confidence band for the multivariable generalized additive model 3. And a for 20-54 years old in male, b for 20-54 years old in female, c for 55-64 years old in male, d for 55-64 years old in female, e for over 65 years old in male, f for over 65 years old in female.

Table4: The smooth function of gout measured by the GAM (Group by age in male and female) (model3)

Smooth terms	EDF	Ref.df	X2	P
Reference (Yes)				
Male				
Spline (Uric Acid): 20-54 years	3.352	4.24	20.01	<0.001
Spline (Uric Acid): 55-64 years	1.795	2.273	12.69	0.002

Spline (Uric Acid): Over 65 years	4.498	5.604	26.78	<0.001
Female				
Spline (Uric Acid): 20-54 years	1	1.001	0.06	0.801
Spline (Uric Acid): 55-64 years	1	1	0.729	0.393
Spline (Uric Acid): Over 65 years	1	1.001	0.51	0.477

Discussion

We used the GAM approach to study 4,846 eligible participants in the 2017-2018 NHANES cycle and found a U-shaped association between SUA levels and gout. This study showed that the risk of gout was high for both males and females with high SUA level. The risk was also high for males with low SUA level. When subjects with different age were focused on, the risk was also high for participants in 20-54years and over 65 years with low or high SUA level. The risk increased with high SUA level in 55-65 years. One study showed that a target SUA between 5.0 and 6.0 mg/dL, appears to be sufficient, which is identical with our finding [24].

Previous study already confirmed that hyperuricemia is a risk factor for gout, which is in agreement with our result [13, 25]. Increased uric acid levels may cause gout [12]. Furthermore, low SUA level was also associated with gout. Congenital hyperuricemia may be caused by many defects in urate transporters. Such patients often have no symptoms; However, they may be more prone to renal failure after strenuous exercise, as well as urate stones [24]. The latest EULAR recommendations for gout care advise against maintaining SUA <3 mg/dL for prolonged periods [26].

Pathogenic mechanisms of hyperuricemia include uric acid overproduction or aberrations of renal uric acid handling resulting in underexcretion [27]. Long-term oversaturated SUA together with sodium can be deposited in joints, soft tissues, bones, skin and other places, acting as MSU crystals to form tophi and trigger gout flares with episodes of severe pain [28]. In addition, SUA can acts as an antioxidant [29]. Low SUA level represents reduced total antioxidant capacity. Therefore, low SUA level may increase the risk of atherosclerotic diseases [30]. A sudden decrease in SUA level may also trigger a gout attack by dissolution of monosodium urate (MSU) from tophi [28].

Furthermore, studies have shown that the occurrence of gout is related to kidney disease [10, 31, 32]. Uric acid is mainly excreted through the kidney, and SUA level in vivo is closely related to renal function [33]. Renal diseases can lead to abnormal uric acid metabolism [34]. Hypouricemia has been shown to increase the risk of worsening kidney function. A prospective cohort study showed a U-shape association between SUA and loss of renal function in healthy subjects [19]. The proposed reasons behind this common and very relevant clinical association are multiple and the association is reciprocal [35]. Therefore, the relationship between SUA level and kidney disease may be a potential cause for the existence of this U-shape association that was found in our study, but further studies are needed to prove this.

In our study we found the clear gender differences in the trend of gout. Previous studies had observed that the clinical course of gout is different between male and female. Male is more likely to present with acute gout than female [36, 37]. Gout in female has a late attack and a long course of disease which has always existed [38]. This is consistent with our results with the linear increase of female and the gradual slowdown of male. Meanwhile, gout is the most common inflammatory arthritis in male [39]. In a previous study that reported NHANES data from 2007-2008, prevalence of gout in male was 5.9% (95% CI: 4.7-7.1) and in female was 2.0% (95% CI: 1.5-2.5) [40]. In different age groups in male and female, female in 55-64 years have a higher prevalence of gout than male. In 20-54 years and over 65 years stage, female is less likely to suffer from gout than male. Our findings were consistent with a study which reported that female have an increased

risk of developing gout after menopause and the risk begins to rise at about age 55 years with the decrease in estrogen levels [41, 42]. Meanwhile, an epidemiologic study has suggested the prevalence of gout increases with advancing age and peaks between ages 75 and 84 years [43].

The different trends between males and females are because estrogen has a urination effect on females, which can reduce the risk of gout. However, The prevalence of gout becomes approximately equal between the sexes after age 60 years [44]. For clinicians, although gout is more common in male, the diagnosis of gout should still consider female, especially postmenopausal female. The findings may provide clinical guidelines on the primary prevention of gout.

There are also limitations in our research. Firstly, our research is an observational study, which cannot infer a causal relationship between SUA level and gout. Secondly, many variables in our study are self-reported. Despite these limitations, our study also has advantages. Firstly, this study used a smoothing curve to explore the non-linear trend between SUA level and gout. Secondly, we assessed the risk of gout at all SUA level in the ordinary population, taking into account both low SUA level and high SUA level. Finally, we assessed the trend of prevalence of gout with SUA level in both male and female grouped by age.

Conclusion

In our study, there is a U-shape association between SUA level and gout. Low SUA level are risk factors for gout in male. Although hypouricemia itself does not appear to pose a health threat to patients, there are potential concerns about overtreatment. At the same time, it is necessary to lose weight appropriately, avoid drinking alcohol (especially beer and spirits) and sugary beverages, avoid large meals and excessive intake of meat and seafood. The use of low-fat dairy products and regular exercise should be encouraged. Further research is needed in the future to track individuals with low SUA levels, elucidate the pathophysiological mechanisms between low SUA levels and gout, and investigate whether interventions that optimize uric acid metabolism or improve total antioxidant capacity are beneficial for the treatment of gout.

Conflict of Interest

The authors have no conflicts of interest or financial ties to disclose.

Author Contributions

YXM and STL were responsible for data extraction, data analyses, model construction and the manuscript writing. LMJ selected the topic, directs the writing, improves the revision. ZZX provided specific knowledge, carried out the literature research. ZHB, ZH, LYR coordinated and managed the operation of the project and the implementation of the project. All authors read and approved the final manuscript.

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Data Availability Statement

Data are available in a public, open access repository. The datasets for this study can be found in https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/index.htm.

Ethics Approval

All NHANES protocols were approved by the National Centre for Health Statistics Research ethics review board.

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