

Comorbidities of Gout and Hyperuricemia in the US General Population: NHANES 2007-2008

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ABSTRACT

PURPOSE: The objective of this study was to estimate the latest prevalence of major comorbidities associated with gout and hyperuricemia in the US based on a recent, nationally representative sample of US men and women.

METHODS: Using data from 5707 participants aged 20 years and older in the National Health and Nutrition Examination Survey 2007-2008, we calculated the national prevalence and population estimates of major comorbidities according to gout status and various hyperuricemia levels, compared with those without these conditions. Case definitions of gout and comorbidities were based on an affirmative answer to a question that asked whether a physician or a health professional had diagnosed the corresponding condition.

RESULTS: Among these individuals with gout, 74% (6.1 million) had hypertension, 71% (5.5 million) had chronic kidney disease stage ≥ 2 , 53% (4.3 million) were obese, 26% (2.1 million) had diabetes, 24% (2.0 million) had nephrolithiasis, 14% (1.2 million) had myocardial infarction, 11% (0.9 million) had heart failure, and 10% (0.9 million) had suffered a stroke. These proportions were substantially higher than those among individuals without gout (all P -values $< .67$). With increasing levels of hyperuricemia, there were graded increases in the prevalences of these comorbidities. In the top category (serum urate ≥ 10 mg/dL), 86% of subjects had chronic kidney disease stage ≥ 2 , 66% had hypertension, 65% were obese, 33% had heart failure, 33% had diabetes, 23% had myocardial infarction, and 12% had stroke. These prevalences were 3-33 times higher than those in the lowest serum urate category (< 4 mg/dL). Sex-specific odds ratios tended to be larger among women than men, and the overall comorbidity prevalence was highest among individuals with both gout and hyperuricemia.

CONCLUSIONS: These findings from the latest nationally representative data highlight remarkable prevalences and population estimates of comorbidities of gout and hyperuricemia in the US. Appropriate preventive and management measures of these comorbidities should be implemented in gout management, with a preference to strategies that can improve gout and comorbidities together.

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Gout is a common and excruciatingly painful inflammatory arthritis caused by hyperuricemia. The disease burden of gout remains substantial and is growing.¹ In addition to

substantial morbidity caused by severe pain and suffering, studies have reported that gout also is associated with several important cardiovascular-metabolic conditions.²⁻⁹ For

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example, a UK general practice cohort study (1990-1999) reported that the prevalences of comorbidities among gout patients were 25% for coronary artery disease, 24% for hypertension, and 6% for diabetes, and their proportions were higher than those among osteoarthritis patients.⁴ Similarly, a study of US veterans (1996 and 1998) reported increased comorbidities in gout patients as compared with those without gout (ie, number of comorbidities, 1.5 vs 0.8, $P < .001$).⁵ An analysis of the US National Health and Nutrition Examination Survey (NHANES) III (1988-1994) also showed that the prevalence of the metabolic syndrome, as defined by the revised National Cholesterol Education Program Adult Treatment Panel III, was 63% among US adults with gout, compared with 25% among individuals without gout.⁶ Similarly, hyperuricemia, the culprit in gout pathogenesis, has been found to be associated with cardiovascular-metabolic conditions,⁷⁻⁹ although it remains unclear whether the association is casual.¹⁰

While the burden of these comorbidities in gout and hyperuricemia in the US may remain substantial in the new millennium, no contemporary national data are available. A substantial presence of these associated comorbidities would add to the overall burden of disease on society, and should be considered in the management of these patients. To address these issues, we analyzed the latest NHANES 2007-2008 and calculated the national prevalence and population estimates of major comorbidities among individuals with gout and various levels of hyperuricemia compared with those without these conditions. Furthermore, we explored the sex-specific effects, as previous studies have suggested that associations with cardiovascular comorbidities may be stronger among women.¹¹⁻¹³

METHODS

Study Population

The NHANES studies are designed to assess the health and nutritional status of adults and children in the US. These studies are based on a representative sample of the non-institutionalized US civilian population that is selected using a multistage, stratified sampling design. The survey is unique in that it combines interviews, physical examinations, and various laboratory data. After a home interview, participants were invited to attend examination sessions where blood and urine specimens were obtained. To estimate the latest prevalence of comorbidities of gout, we used the NHANES 2007-2008 data, which was the first and only survey that asked about presence of gout since NHANES

III, which was conducted between 1988 and 1994. We also used the NHANES 2007-2008 serum uric acid data in our analysis in order to provide the same calendar-year estimates as gout estimates. These analyses included 5707 participants (2797 men and 2910 women) aged 20 years and older, for whom interview, examination, and laboratory data were available in the NHANES 2007-2008.

Additionally, serum urate data have been collected in all other NHANES studies conducted between 1999 and 2008; thus, we also analyzed the combined 10-year NHANES data for more precise estimates related to serum urate levels. This analysis was derived from 24,693 participants (11,816 men and 12,877 women) aged 20 years and older in NHANES 1999-2008, on whom interview, examination, and laboratory data were available.

CLINICAL SIGNIFICANCE

- According to the latest nationally representative data, prevalences and population estimates of major comorbidities of gout and hyperuricemia in the US are remarkably high.
- Appropriate preventive and management measures of these comorbidities should be implemented in gout management.
- The lifestyle and pharmacologic measures that can improve serum uric acid and comorbidities together should be preferred.

Assessment of Gout and Comorbidities

During the home interviews of NHANES 2007-2008, all subjects were asked, "Has a doctor or other health professional ever told you that you had gout?" All subjects were asked similar questions to assess the comorbidities of interest, including hypertension ("Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?"), nephrolithiasis ("Have you ever had kidney stones?"), type 2 diabetes mellitus ("Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?"), myocardial infarction ("Has a doctor or other health professional ever told you that you had a heart attack [also called myocardial infarction]?"), heart failure ("Has a doctor or other health professional ever told you that you had congestive heart failure?"), and stroke ("Has a doctor or other health professional ever told you that you had a stroke?"). Body mass index was calculated by dividing subjects' weight in kilograms by the square of their height in meters. Obesity was defined as body mass index ≥ 30 kg/m². Glomerular filtration rate (GFR) was estimated by using the simplified Modification of Diet in Renal Disease study equation: $GFR \text{ (mL/min per } 1.73 \text{ m}^2) = 186 \times (\text{serum creatinine level [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times [0.742, \text{ if female}] \times [1.212, \text{ if black}]$.¹⁴⁻¹⁶ We estimated the prevalence of chronic kidney disease stage ≥ 2 (GFR < 60 mL/min per 1.73 m²) and chronic kidney disease stage ≥ 3 (GFR < 30 mL/min per 1.73 m²). For our analyses of NHANES 1999-2008, we used the same definitions of these conditions, except for gout and nephrolithiasis, on which data were obtained only in NHANES 2007-2008.

Serum Urate Measurement and Definitions of Hyperuricemia

In NHANES 1999-2008, serum urate level was measured by oxidization with the specific enzyme uricase to form allantoin and H₂O₂. Details of quality-control procedures have been published elsewhere (<http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf>). Values are reported in milligrams per deciliter (mg/dL) and can be converted to micromoles per liter ($\mu\text{mol/L}$) by multiplying by 59.48. Our primary definition of hyperuricemia was serum urate level >7.0 mg/dL among men and serum urate level >5.7 mg/dL among women.¹⁷ We also examined the potential impact of alternative definitions of hyperuricemia by categorizing serum urate level into 1-mg/dL increments in the combined NHANES data (1999-2008), as they allowed bigger sample sizes in each serum urate level category.

Statistical Analysis

All statistical analyses were performed using survey commands of STATA (ie, SVY) to adjust for clusters and strata of the complex sample design as well as to incorporate sample weights (version 11.1; StataCorp LP, College Station, Tex). These procedures generated estimates for the total civilian, noninstitutionalized population of the US. We calculated the national prevalence and population estimates of comorbidities among individuals with gout. We then performed logistic regression analyses to quantify the magnitude of association between the presence of gout and the presence of comorbidities, and calculated odds ratios (ORs). These analyses were then repeated according to hyperuricemia and increasing serum urate levels. We also estimated the prevalence of comorbidities according to both gout status and hyperuricemia. Finally, we explored potential interactions by sex by testing the significance of interaction terms added to our final models. For the interaction analyses between serum urate level and sex, we used serum urate level as a continuous variable. For all measures, we calculated 95% confidence intervals (CIs). All reported *P* values are 2-sided.

RESULTS

Comorbidities of Gout in the US in 2007-2008

In the NHANES 2007-2008, the mean age was 47 years, 48.2% of subjects were male, and 69.4% were white. Overall, 3.9% of US adults reported a physician or health professional diagnosis of gout. Among these individuals with gout, 74% (6.1 million) had hypertension, 71% (5.5 million) had chronic kidney disease stage ≥ 2 , 53% (4.3 million) were obese, 26% (2.1 million) had diabetes, 24% (2.0 million) had nephrolithiasis, 14% (1.2 million) had myocardial infarction, 11% (0.9 million) had heart failure, and 10% (0.9 million) had stroke (**Table 1**). These proportions were substantially higher than those among individuals without gout,

and the age- and sex-adjusted ORs ranged from 4.19 (95% CI, 2.75-6.39) for hypertension to 1.75 (95% CI, 1.23-2.49) for chronic kidney disease stage ≥ 2 (**Table 1**).

In our analyses stratified by sex, comorbidities tended to be more frequent among women with gout than men with gout, except for obesity, nephrolithiasis, and chronic kidney disease stage ≥ 2 (**Table 1**). Age-adjusted ORs for heart failure were 5.84 among women and 1.72 among men (*P* for interaction <.001), and those for myocardial infarction were 6.86 among women and 1.45 among men (*P* for interaction = .012) (**Table 1**). Similarly, age-adjusted ORs for diabetes were 4.23 among women and 1.73 among men (*P* for interaction = .006) (**Table 1**).

Comorbidities of Hyperuricemia in the US in 2007-2008 and in 1999-2008

To provide the same calendar years' estimates as the gout data above, we first examined the prevalence of comorbidities among US adults with hyperuricemia in the NHANES 2007-2008. The overall prevalence of hyperuricemia (serum urate level >7.0 mg/dL among men and serum urate level >5.7 mg/dL among women) among US adults was 21.4% (21.1% among men and 21.6% among women). The overall mean serum urate level was 6.14 mg/dL (95% CI, 6.06-6.23 mg/dL) among men and 4.87 mg/dL (95% CI, 4.79-4.94 mg/dL) among women. Among individuals with hyperuricemia, 61% had chronic kidney disease stage ≥ 2 , 54% were obese, 50% had hypertension, 14% had diabetes, 12% had nephrolithiasis, 6% had stroke, 5% had myocardial infarction, and 5% had heart failure (**Table 2**). When we examined these comorbidities using the same definitions of hyperuricemia in the NHANES data combining 5 surveys (1999-2008), results were similar.

We also analyzed the comorbidities according to serum urate level categories with 1-mg/dL increments in the combined NHANES data (1999-2008), as they allowed bigger sample sizes in each serum urate level category (**Table 3**). With increasing levels of hyperuricemia, there were graded increases in the prevalences of these comorbidities. In the highest serum urate level category (≥ 10 mg/dL), prevalence was 86% for chronic kidney disease stage ≥ 2 , 66% for hypertension, 65% for obesity, 33% for heart failure, 33% for diabetes, 23% for myocardial infarction, and 12% for stroke (**Table 3**). Our analysis limited to the NHANES 2007-2008 data showed similar findings (**Supplemental Table**).

In our sex-stratified analyses of serum urate level outcomes, the prevalences of comorbidities were higher among women with higher serum urate level than among men in the same serum urate level categories (**Table 3**). A significant sex interaction (greater prevalence in women) was present for hypertension, obesity, and diabetes (*P* values for interaction <.02) in NHANES 2007-2008 (**Table 2**) and for hypertension, obesity, diabetes, heart failure, and chronic kidney disease stage ≥ 3 (*P* values for interaction <.04) in NHANES 1999-2008 (**Table 3**).

Table 1 Prevalence of Comorbidities According to Presence of Gout, NHANES 2007-2008

Comorbidities*	Gout		No Gout	Age-† and Sex-adjusted OR (95% CI)	P Value for Interaction by Sex
	Population Estimates (in Millions)	Prevalence, % (95% CI)	Prevalence, % (95% CI)		
Hypertension	6.1	73.9 (67.9-79.9)	28.9 (26.6-31.2)	4.19 (2.75-6.39)	.55
Men	4.4	71.5 (63.2-79.8)	27.2 (23.6-30.7)	4.02 (2.27-7.13)	
Women	1.7	80.6 (68.4-92.8)	30.5 (27.8-33.1)	5.18 (2.54-10.55)	
CKD stage ≥ 2 (GFR <60)	5.5	71.1 (65.4-76.8)	42.1 (38.0-46.1)	1.75 (1.23-2.49)	.42
Men	4.1	72.1 (63.4-80.7)	38.9 (34.1-43.6)	2.04 (1.17-3.56)	
Women	1.3	68.2 (50.0-86.4)	44.9 (40.5-49.3)	1.13 (0.40-3.22)	
Obesity (BMI ≥ 30 kg/m ²)	4.3	53.3 (44.8-61.9)	32.8 (30.3-35.3)	2.35 (1.55-3.57)	.48
Men	3.2	53.3 (44.0-62.5)	30.7 (27.4-34.0)	2.32 (1.46-3.70)	
Women	1.1	53.5 (41.4-65.6)	34.8 (32.3-37.2)	2.18 (1.24-3.82)	
Diabetes	2.1	25.7 (15.8-35.6)	7.8 (6.3-9.3)	2.36 (1.49-3.73)	.006
Men	1.3	20.6 (12.5-28.8)	7.6 (6.3-8.9)	1.73 (1.06-2.83)	
Women	0.8	39.4 (22.9-55.9)	8.1 (5.8-10.3)	4.23 (2.47-7.23)	
Nephrolithiasis	2.0	23.8 (16.8-30.7)	8.4 (7.1-9.6)	2.10 (1.39-3.18)	.54
Men	1.7	27.3 (17.7-36.8)	10.6 (8.8-12.4)	2.09 (1.16-3.76)	
Women	0.3	14.0 (5.1-22.8)	6.4 (5.1-7.7)	1.83 (0.79-4.21)	
CKD stage ≥ 3 (GFR <30)	1.5	19.9 (15.4-24.3)	5.2 (4.1-6.4)	2.32 (1.65-3.26)	.61
Men	0.9	16.0 (10.9-21.1)	3.8 (2.2-5.4)	2.16 (1.10-4.24)	
Women	0.6	31.4 (17.9-45.0)	6.5 (5.2-7.9)	2.82 (1.19-6.71)	
Myocardial infarction	1.2	14.4 (10.0-18.7)	2.9 (2.2-3.5)	2.37 (1.54-3.65)	.012
Men	0.7	11.5 (8.2-14.8)	3.8 (2.7-4.9)	1.45 (0.82-2.54)	
Women	0.5	22.1 (10.6-33.7)	2.0 (1.5-2.6)	6.86 (2.87-16.41)	
Heart failure	0.9	11.2 (6.9-15.5)	2.0 (1.5-2.6)	2.68 (1.88-3.83)	<.001
Men	0.5	8.3 (6.0-10.6)	2.3 (1.7-2.8)	1.72 (1.17-2.54)	
Women	0.4	19.1 (8.0-30.3)	1.8 (1.1-2.6)	5.84 (3.59-9.51)	
Stroke	0.9	10.4 (3.8-17.0)	2.9 (2.2-3.6)	2.02 (0.98-4.19)	.67
Men	0.5	8.3 (3.0-13.7)	2.3 (1.8-2.9)	1.86 (0.67-5.16)	
Women	0.4	16.0 (0-32.8)	3.4 (2.2-4.6)	2.37 (0.81-6.92)	

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73 m²); NHANES = US National Health and Nutrition Examination Survey; OR = odds ratio.

*Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with gout.

†For sex-specific data, age-adjusted estimates were provided.

Comorbidities among Those with Both Gout and Hyperuricemia in the US in 2007-2008

Among the US adults with both gout and hyperuricemia, 78% had hypertension, 72% had chronic kidney disease stage ≥ 2 , 56% were obese, 27% had diabetes, 20% had nephrolithiasis, 12% had myocardial infarction, 12% had heart failure, and 12% had stroke (**Table 4**). These prevalences were substantially higher than those among individuals without gout or hyperuricemia. Among individuals without gout, hyperuricemia also was associated with a higher prevalence of comorbidities compared with subjects with a normal serum urate level. A similar trend was observed among individuals with gout, although smaller sample sizes in corresponding strata did not allow for a precise comparison.

DISCUSSION

In this recent, nationally representative sample of US men and women, we found that the prevalence of comorbidities of gout was substantial. Approximately 74% of US adults with gout

had hypertension, 71% had chronic kidney disease stage ≥ 2 , 53% were obese, 26% had diabetes, 24% had nephrolithiasis, 14% had a myocardial infarction, and 11% had heart failure. These prevalences were 2-3 times higher than among those without gout. Correspondingly, we found that with increasing levels of hyperuricemia, there were graded increases in these comorbidities. In the highest serum urate level category (≥ 10 mg/dL), prevalences were 86% for chronic kidney disease stage ≥ 2 , 66% for hypertension, 65% for obesity, 33% for diabetes, 23% for myocardial infarction, and 33% for heart failure. These prevalences were 3-33 times higher than those of adults with the lowest serum urate level (<4 mg/dL). These associations tended to be stronger among women than among men. Our findings highlight the continued substantial presence of comorbidities among US individuals with gout or hyperuricemia in the new millennium.

There are several important implications of our results. The prevalence estimates determined in the current study provide the probabilities of presence of these comorbidities

Table 2 Prevalence of Comorbidities among Participants with or without Hyperuricemia, NHANES 2007-2008

Comorbidities*	Hyperuricemia		No Hyperuricemia	Age-† and Sex-adjusted OR (95% CI)	P Value for Interaction by Sex
	Population Estimates (in Millions)	Prevalence, % (95% CI)	Prevalence, % (95% CI)		
CKD stage ≥ 2 (GFR < 60)	26.6	61.4 (56.1-66.7)	38.2 (34.5-41.9)	2.33 (1.94-2.80)	.23
Men	11.8	57.2 (50.9-63.5)	36.4 (32-40.7)	2.63 (2.01-3.43)	
Women	14.8	65.2 (58.9-71.6)	39.8 (36-43.7)	2.08 (1.61-2.70)	
Obesity (BMI ≥ 30 kg/m ²)	23.1	54.4 (50.1-58.8)	27.6 (24.5-30.7)	3.12 (2.43-4.01)	.02
Men	9.9	49.0 (44.4-53.6)	27.7 (24.1-31.2)	2.49 (1.99-3.13)	
Women	13.2	59.4 (53.2-65.5)	27.5 (24.0-30.9)	4.11 (2.85-5.93)	
Hypertension	21.5	49.7 (45.8-53.7)	25.5 (23.0-28.0)	2.60 (2.15-3.14)	.002
Men	8.3	40.0 (33.5-46.5)	27.6 (24.0-31.1)	1.76 (1.33-2.33)	
Women	13.2	58.6 (52.5-64.8)	23.5 (20.9-26.0)	3.74 (2.76-5.08)	
CKD stage ≥ 3 (GFR < 30)	6.4	14.8 (10.9-18.8)	3.3 (2.7-3.9)	3.96 (2.63-5.97)	.09
Men	1.9	9.4 (5.5-13.2)	3.2 (2.2-4.2)	3.14 (1.92-5.13)	
Women	4.5	19.9 (15.3-24.4)	3.4 (2.6-4.3)	4.57 (2.93-7.14)	
Diabetes	5.8	13.5 (9.3-17.7)	7.1 (5.9-8.3)	1.63 (1.13-2.34)	.02
Men	2.0	9.5 (5.8-13.2)	8.2 (6.7-9.8)	1.08 (0.60-1.93)	
Women	3.8	17.2 (11.9-22.4)	6.0 (4.1-7.9)	2.32 (1.67-3.23)	
Nephrolithiasis	5.3	12.3 (9.8-14.8)	8.3 (7.1-9.5)	1.40 (1.07-1.83)	.13
Men	2.8	13.6 (8.7-18.5)	11.5 (9.8-13.1)	1.16 (0.76-1.76)	
Women	2.5	11.1 (8.0-14.2)	5.3 (4.2-6.3)	1.97 (1.34-2.91)	
Stroke	2.4	5.7 (3.8-7.6)	2.4 (1.5-3.3)	1.74 (1.16-2.59)	.24
Men	0.7	3.6 (2.2-5.0)	2.4 (1.8-3.1)	1.37 (0.75-2.48)	
Women	1.7	7.6 (4.4-10.8)	2.4 (1.0-3.8)	2.02 (1.22-3.33)	
Myocardial infarction	2.2	5.1 (4.1-6.0)	2.8 (2.1-3.4)	1.45 (1.12-1.88)	.33
Men	1.1	5.3 (3.4-7.2)	4.0 (2.8-5.2)	1.21 (0.79-1.84)	
Women	1.1	4.9 (3.6-6.1)	1.6 (1.0-2.2)	1.95 (1.08-3.53)	
Heart failure	2.2	5.1 (3.8-6.4)	1.6 (1.0-2.1)	2.52 (1.58-4.04)	.25
Men	0.9	4.6 (2.7-6.5)	2.1 (1.4-2.8)	2.07 (1.17-3.65)	
Women	1.3	5.6 (3.7-7.4)	1.1 (0.3-1.8)	3.21 (1.56-6.58)	

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73 m²); NHANES = US National Health and Nutrition Examination Survey; OR = odds ratio.

*Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with hyperuricemia.

†For sex-specific data, age-adjusted estimates were provided.

among individuals with gout corresponding to differing degrees of hyperuricemia, in recent years. The presence of gout or hyperuricemia, particularly at higher levels, should trigger a high level of clinical suspicion and investigation for the potential coexistence of these comorbidities. If present, comorbidities need to be recognized as factors potentially more life-threatening than gout or hyperuricemia,¹⁸ and must be appropriately managed.

Management of gout or hyperuricemia (particularly long-term) should take into account these frequent comorbidities, as some short-term antigout measures could lead to or worsen these concurrent conditions. For example, conventional dietary recommendations for hyperuricemia or gout have focused almost exclusively on restriction of purine intake, although low-purine diets are often high in refined carbohydrates (including fructose) and saturated fat.¹⁹ These macronutrients are associated with an increased risk of the insulin resistance syndrome and associated major consequences.²⁰⁻²⁴ Furthermore, these macronutrients tend

to lead to higher serum insulin levels, which are known to reduce renal excretion of urate,^{21,25-27} thus potentially further contributing to hyperuricemia in the long run. Thus, it is essential to develop appropriate lifestyle guidelines that take into account improving hyperuricemia as well as overall long-term health effects. Furthermore, because hyperuricemia, gout, and comorbidities could share components of prevention and management approaches, desirable management strategies should be those that aim at improving gout and its comorbidities together.²⁸ For example, among gout patients with concurrent hypertension (74% of gout patients in the US, **Table 1**), antihypertensive agents with uricosuric properties (for example, losartan²⁹ or amlodipine³⁰) could have a substantially better risk-benefit ratio than diuretics.

Gout and hyperuricemia tended to have stronger associations with comorbidities among women than among men. This trend is consistent with sex-specific, longitudinal cohort studies of several cardiovascular outcomes.¹¹⁻¹³ Substantial sex differences in baseline serum urate levels,^{31,32}

Table 3 Prevalence of Comorbidities According to Serum Urate Level (SUL) Categories, NHANES 1999-2008

Comorbidities*	Serum Urate Levels (mg/dL)			
	<4	4-4.9	5-5.9	6-6.9
CKD stage ≥ 2 (GFR < 60)	31.9 (29.4-34.5)	42.7 (40.2-45.2)	49.2 (46.1-52.2)	52.5 (50.0-54.9)
OR (95% CI)	1.0 (Referent)	1.59 (1.40-1.80)	2.06 (1.79-2.37)	2.35 (2.06-2.69)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.55 (1.34-1.80)	2.22 (1.91-2.59)	2.86 (2.45-3.35)
Men	34.1 (27.9-40.2)	35.7 (32-39.5)	42.9 (39.3-46.5)	47.3 (44.7-49.8)
Women	31.7 (29.0-34.5)	45.4 (42.7-48.1)	57.0 (53.6-60.4)	65.6 (62.1-69.0)
Hypertension	16.9 (14.9-18.8)	22.7 (21.3-24.2)	30.2 (28.3-32.1)	34.4 (32.2-36.5)
OR (95% CI)	1.0 (Referent)	1.45 (1.26-1.68)	2.13 (1.85-2.45)	2.58 (2.21-3.02)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.39 (1.20-1.61)	2.23 (1.93-2.57)	3.03 (2.56-3.59)
Men	27.2 (20.9-33.6)	22.6 (19.6-25.5)	24.3 (22.0-26.5)	27.3 (24.9-29.7)
Women	15.8 (13.9-17.8)	22.8 (21.1-24.6)	37.5 (34.8-40.2)	52.1 (48.4-55.7)
Obesity (BMI ≥ 30 kg/m ²)	16.9 (15.2-18.6)	24.1 (22.5-25.7)	34.0 (32.1-35.8)	41.2 (38.9-43.5)
OR (95% CI)	1.0 (Referent)	1.56 (1.36-1.79)	2.52 (2.20-2.89)	3.44 (3.04-3.89)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.80 (1.56-2.09)	3.77 (3.24-4.38)	6.00 (5.22-6.91)
Men	17.7 (12.9-22.5)	16.9 (14.1-19.7)	23.9 (21.8-25.9)	34.2 (31.6-36.8)
Women	16.9 (15.1-18.6)	26.9 (24.9-28.8)	46.7 (44.3-49.2)	59.0 (55.0-63.0)
CKD stage ≥ 3 (GFR < 30)	1.4 (0.9-1.8)	3.1 (2.6-3.7)	5.1 (4.4-5.9)	8.1 (6.9-9.2)
OR (95% CI)	1.0 (Referent)	2.32 (1.55-3.47)	3.92 (2.62-5.85)	6.34 (4.2-9.56)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	2.18 (1.40-3.38)	3.87 (2.44-6.15)	7.52 (4.77-11.86)
Men	2.3 (0.9-3.7)	2.3 (1.4-3.3)	2.8 (2.1-3.4)	4.2 (3.3-5)
Women	1.3 (0.8-1.8)	3.4 (2.8-4)	8.1 (6.8-9.4)	17.9 (15.1-20.6)
Heart failure	1.0 (0.6-1.4)	1.7 (1.3-2.0)	1.8 (1.3-2.2)	2.5 (2.0-3.1)
OR (95% CI)	1.0 (Referent)	1.64 (1.01-2.67)	1.73 (1.08-2.76)	2.51 (1.59-3.96)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.33 (0.82-2.17)	1.20 (0.75-1.91)	1.68 (1.05-2.70)
Men	4.0 (1.2-6.8)	2.3 (1.5-3.1)	1.7 (1.2-2.3)	1.9 (1.3-2.5)
Women	0.7 (0.4-1.1)	1.4 (1.0-1.9)	1.8 (1.2-2.4)	4.1 (2.7-5.5)
Diabetes	7.6 (6.5-8.7)	10.4 (9.3-11.5)	12.1 (10.7-13.5)	13.5 (12.4-14.7)
OR (95% CI)	1.0 (Referent)	1.18 (0.96-1.44)	1.20 (0.97-1.48)	1.34 (1.08-1.66)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.02 (0.83-1.26)	0.96 (0.76-1.20)	1.06 (0.83-1.35)
Men	17.5 (12.7-22.4)	10.6 (8.7-12.4)	6.7 (5.7-7.8)	5.9 (4.9-6.8)
Women	5.0 (4.0-5.9)	5.8 (4.9-6.7)	7.9 (6.6-9.2)	13.5 (11.2-15.9)
Myocardial infarction	1.7 (1.0-2.4)	2.4 (1.9-2.8)	3.2 (2.8-3.7)	3.8 (2.9-4.7)
OR (95% CI)	1.0 (Referent)	1.41 (0.93-2.15)	1.93 (1.24-2.99)	2.27 (1.38-3.71)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.06 (0.69-1.64)	1.16 (0.73-1.83)	1.26 (0.76-2.06)
Men	4.8 (2.1-7.4)	3.9 (2.7-5.0)	3.6 (2.9-4.3)	3.8 (2.7-4.9)
Women	1.4 (0.8-2.0)	1.8 (1.3-2.3)	2.8 (2.0-3.6)	3.7 (2.6-4.8)
Stroke	1.8 (1.2-2.4)	2.5 (1.9-3.0)	2.6 (2.1-3.1)	2.4 (2.0-2.9)
OR (95% CI)	1.0 (Referent)	1.37 (0.96-1.96)	1.44 (0.98-2.1)	1.35 (0.93-1.94)
Age- and sex-adjusted OR (95% CI)	1.0 (Referent)	1.20 (0.82-1.76)	1.20 (0.80-1.79)	1.13 (0.77-1.66)
Men	2.0 (0.7-3.4)	2.4 (1.7-3.2)	2.1 (1.5-2.7)	1.7 (1.2-2.1)
Women	1.8 (1.2-2.4)	2.5 (1.7-3.3)	3.2 (2.3-4.1)	4.4 (3.1-5.6)

BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73 m²); NHANES = US National Health and Nutrition Examination Survey; OR = odds ratio.

*Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with highest serum urate levels (≥ 10 mg/dL).

†Categories collapsed due to small sample sizes.

and perhaps uric acid metabolism,³² may explain the stronger associations of several cardiovascular-metabolic conditions associated with gout or hyperuricemia among women, compared with men. Serum urate levels in men are about 1 mg/dL higher than in women in adulthood, although levels in women increase around natural menopause.^{31,32} Thus, the relative physiologic impact of having gout or a certain degree of hyperuricemia may be stronger among women than men.¹³

Strengths and limitations of our study deserve comment. This study was performed using the latest nationally representative sample of US women and men; thus, the findings are likely to be generalizable to the current US population. The current study provides national estimates of the prevalence of comorbidities among individuals with gout and those with different serum urate levels, a finding that the NHANES cross-sectional study design was well suited to address. However, the current

Table 3 Continued

7-7.9	8-8.9	9-9.9	≥10	P Value for Interaction by Sex (Continuous SUL)
58.2 (55.3-61.1)	66.4 (61.8-71.0)	74.0 (65.4-82.7)	85.9 (77.3-94.5)	.103
2.97 (2.51-3.51)	4.21 (3.48-5.10)	6.08 (3.97-9.30)	12.98 (6.41-26.30)	
3.67 (3.06-4.41)	5.21 (4.09-6.64)	6.09 (3.41-10.88)	11.31 (4.90-26.13)	
53.5 (50.4-56.6)	61.4 (56.1-66.7)	68.9 (58.2-79.6)	84.7 (74.7-94.7)	
78.6 (73.8-83.3)	87.9 (80.9-94.9)	91.1 (82.9-99.3)	88.8 (73.7-103.9)	
41.4 (38.6-44.1)	50.0 (44.2-55.7)	67.2 (59.3-75.2)	66.0 (52.6-79.4)	<.001
3.48 (2.98-4.06)	4.92 (3.81-6.36)	10.11 (6.76-15.12)	9.56 (5.33-17.17)	
4.20 (3.53-4.99)	5.89 (4.33-8.00)	10.70 (6.91-16.55)	7.68 (3.35-17.59)	
34.3 (31.1-37.4)	42.5 (36.4-48.7)	58.4 (49.2-67.6)	64.6 (49.7-79.5)	
71.8 (65.2-78.4)	81.7 (73.7-89.8)	87.5† (76.6-98.4)		
46.3 (43.3-49.4)	52.9 (48.7-57.0)	56.6 (48.1-65.2)	65.3 (53.6-77.0)	.001
4.24 (3.62-4.96)	5.50 (4.56-6.63)	6.40 (4.32-9.49)	9.23 (5.60-15.21)	
8.13 (6.71-9.86)	10.66 (8.64-13.14)	12.35 (8.10-18.84)	16.59 (10.06-27.35)	
42.9 (39.4-46.5)	50.8 (45.7-55.8)	52.2 (42.9-61.6)	60.6 (43.9-77.2)	
61.2 (55.1-67.3)	62.1 (53.1-71.0)	73.6 (60.5-86.8)	75.8 (56.4-95.1)	
11.7 (10.3-13.2)	20.2 (17.2-23.2)	40.6 (32.2-49.1)	53.5 (39.2-67.7)	.04
9.6 (6.51-14.16)	18.29 (12.13-27.57)	49.47 (28.55-85.73)	83.01 (41.49-166.06)	
12.44 (7.69-20.11)	26.46 (16.00-43.77)	67.96 (34.13-135.33)	106.48 (42.37-267.61)	
6.7 (5.3-8.0)	12.4 (10.2-14.6)	36.4 (27.0-45.8)	46.6 (31.2-62.0)	
33.7 (29.1-38.2)	53.4 (42.9-64)	54.8 (35.8-73.8)	69.8 (44.8-94.8)	
4.4 (3.3-5.5)	6.4 (4.5-8.2)	13.4 (7.8-18.9)	32.9 (20.2-45.6)	.04
4.43 (2.92-6.72)	6.58 (3.91-11.08)	14.86 (8.12-27.19)	47.29 (24.97-89.58)	
2.72 (1.73-4.28)	3.75 (2.16-6.50)	6.08 (3.00-12.34)	19.59 (10.08-38.07)	
3.6 (2.5-4.7)	5.3 (3.3-7.4)	12.6 (6.5-18.8)	25.0 (13.3-36.6)	
7.9 (4.7-11.0)	10.8 (6.0-15.7)	15.7 (4.1-27.4)	51.8 (21.6-81.9)	
15.9 (14.3-17.6)	20.6 (17-24.2)	29.1 (20.9-37.2)	32.6 (20.7-44.4)	<.001
1.41 (1.09-1.81)	2.01 (1.43-2.83)	4.67 (2.81-7.75)	7.33 (4.00-13.43)	
1.04 (0.77-1.40)	1.41 (0.96-2.07)	2.70 (1.50-4.84)	3.77 (1.75-8.10)	
6.3 (5.0-7.7)	8.9 (6.0-11.8)	17.0 (8.5-25.6)	27.3 (11.7-43.0)	
17.4 (12.5-22.2)	23.3 (15.1-31.5)	44.6 (27.0-62.2)	44.4 (21.1-67.8)	
5.9 (4.6-7.1)	7.8 (5.9-9.7)	16.1 (9.6-22.5)	23.1 (14.3-31.9)	.68
3.59 (2.22-5.82)	4.89 (2.98-8.03)	11.06 (6.16-19.87)	17.36 (9.39-32.11)	
1.76 (1.09-2.86)	2.26 (1.37-3.72)	3.77 (2.04-6.96)	5.33 (2.67-10.61)	
5.6 (4.2-7.0)	7.4 (5.3-9.5)	13.6 (7.7-19.4)	20.3 (11.2-29.5)	
7.1 (4.2-10.0)	9.5 (5.2-13.9)	24.5 (7.1-41.8)	29.7 (7.8-51.7)	
4.4 (3.2-5.6)	4.6 (2.8-6.4)	11.8 (7.3-16.4)	11.7 (5.0-18.4)	.49
2.51 (1.73-3.65)	2.62 (1.51-4.56)	7.27 (4.46-11.84)	7.21 (3.31-15.66)	
2.05 (1.36-3.10)	1.90 (1.03-3.52)	3.98 (2.21-7.15)	3.09 (1.38-6.94)	
3.1 (2.2-4.0)	3.0 (1.4-4.5)	8.5 (4.2-12.8)	10.3 (2.8-17.7)	
10.2 (6.0-14.5)	11.6 (5.2-17.9)		20.3† (8.3-32.3)	

cross-sectional design is not able to address potential temporal relations between hyperuricemia and these comorbidities, which need to be addressed by longitudinal studies. The self-reported diagnosis of gout by a physician was not validated in this study. However, it is unlikely that misclassification of the diagnosis would explain the strong associations observed in this population study. It remains conceivable that the results may be even more striking with more specific case definitions of gout, as was the case in our prospective epidemiologic study of gout for suspected associated factors.^{33,34} Furthermore, the serum urate level-derived variables in our

study were ascertained objectively without reliance on study participants' recall, and showed consistent results.

In conclusion, these findings from the latest nationally representative data highlight remarkable prevalences and population estimates of comorbidities of gout and hyperuricemia in the US. These comorbidities add to the overall illness burden of gout and hyperuricemia on society. Given the serious complications associated with these comorbidities, these conditions should be recognized and taken into account in the long-term management and overall health of individuals with gout and hyperuricemia. The lifestyle and pharmacologic measures that can

Table 4 Prevalence of Comorbidities According to Hyperuricemia and Gout in NHANES 2007-2008

Comorbidities* Prevalence, % (95% CI)	Gout		No Gout	
	Hyperuricemia	No Hyperuricemia	Hyperuricemia	No Hyperuricemia
Hypertension	77.7 (66.6-88.8)	70.8 (60.8-80.8)	47.2 (43.0-51.4)	24.3 (21.8-26.7)
CKD stage ≥ 2 (GFR < 60)	71.8 (61.3-82.3)	60.5 (54.8-66.2)	70.4 (62.8-78.0)	37.3 (33.7-41.0)
Obesity (BMI ≥ 30 kg/m ²)	55.6 (45.5-65.7)	50.2 (35.7-64.7)	54.2 (49.0-59.4)	27.0 (23.9-30.1)
Diabetes	26.9 (9.7-44.1)	21.4 (14.9-28.0)	12.2 (8.7-15.6)	6.7 (5.4-8.1)
CKD stage ≥ 3 (GFR < 30)	22.6 (14.0-31.2)	14.1 (10.1-18.2)	17.4 (13.2-21.5)	2.9 (2.3-3.6)
Nephrolithiasis	20.2 (10.3-30.2)	26.2 (15.6-36.9)	11.6 (8.9-14.3)	7.8 (6.7-8.8)
Stroke	11.8 (0.4-23.1)	8.0 (3.3-12.7)	5.1 (3.6-6.7)	2.3 (1.4-3.1)
Heart failure	11.7 (6.1-17.4)	8.2 (4.4-12.0)	4.5 (3.4-5.5)	1.4 (0.8-2.0)
Myocardial infarction	11.6 (4.5-18.7)	14.1 (10.9-17.3)	4.5 (3.3-5.6)	2.5 (1.8-3.1)

BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73 m²); NHANES = US National Health and Nutrition Examination Survey.

*Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with gout and hyperuricemia.

improve serum urate level and comorbidities together should be preferred.

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Supplemental Table Prevalence of Comorbidities According to Serum Urate Level Categories, NHANES 2007-2008

Comorbidities*	Serum Urate Levels (mg/dL)							
	<4	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-9.9	≥10
CKD stage ≥2 (GFR <60)	28.2 (22.3-34.1)	38.5 (33.7-43.4)	42.9 (37.2-48.6)	45.4 (40.1-50.6)	58.1 (50.9-65.2)	65.1 (56.2-73.9)	76.6 (59.4-93.8)	91.6 (82.4-100.8)
Hypertension	16.7 (12.0-21.5)	22.2 (19.6-24.8)	32.1 (28.8-35.5)	36.3 (31.8-40.7)	42.2 (36.7-47.7)	49.3 (34.9-63.6)	70.3 (53.4-87.3)	83.8 (70.2-97.3)
Obesity (BMI ≥30 kg/m ²)	17.3 (13.0-21.5)	23.5 (20.7-26.4)	34.5 (30.2-38.9)	40.8 (35.8-45.9)	49.0 (43.5-54.5)	53.6 (47.2-60.0)	62.9 (46.7-79.1)	68.9 (52.5-85.4)
Diabetes	7.6 (4.5-10.6)	6.9 (4.9-8.9)	8.1 (6.2-10.0)	8.3 (6.1-10.4)	11.5 (7.2-15.7)	9.7 (3.8-15.5)	20.9 (4.7-37.2)	48.2 (25.8-70.5)
CKD stage ≥3 (GFR <30)	1.5 (0.2-2.7)	3.6 (2.4-4.8)	4.1 (3.1-5.2)	7.3 (4.9-9.6)	10.4 (7.4-13.5)	15.0 (9.6-20.5)	36.2 (19.7-52.7)	46.1 (22.2-70.0)
Heart failure	1.2 (0.2-2.1)	1.9 (1.1-2.6)	1.5 (0.7-2.3)	2.4 (1.7-3.1)	3.0 (1.8-4.2)	7.8 (3.0-12.6)	13.3 (2.9-23.7)	28.2 (6.7-49.7)
Myocardial infarction	1.3 (0.3-2.2)	2.9 (1.8-3.9)	3.3 (2.2-4.3)	3.3 (2.1-4.5)	4.0 (2.9-5.1)	7.4 (2.8-11.9)	9.7 (1.9-17.4)	18.5 (3.0-34.0)
Nephrolithiasis	4.6 (2.8-6.3)	8.1 (6.1-10.0)	8.4 (6.5-10.4)	12.1 (9.7-14.6)	10.8 (6.5-15.1)	15.6 (8.5-22.8)		12.9† (3.6-22.2)
Stroke	1.8 (0.7-3)	2.9 (1.5-4.4)	2.5 (1.3-3.7)	3.1 (2.2-3.9)	5.5 (2.4-8.5)	3.7 (0.3-7.1)		12.1† (3.4-20.8)

BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73 m²); NHANES = US National Health and Nutrition Examination Survey.

*Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with highest serum urate levels (≥10 mg/dL).

†Categories collapsed due to small sample sizes.