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The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

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Running Head: Association between asymptomatic hyperuricemia and risk of arthritis.

Abstract

Background

Arthritis is thought to be closely related to serum uric acid. The study aims to assess the association between asymptomatic hyperuricemia (AH) and arthritis.

Methods

A multistage, stratified cluster was used to conduct a cross-sectional study of adult U.S. civilians aged≥ 20 years from the 2007-2018 National Health and Nutrition Examination Survey (NHANES). Participants with hyperuricemia and without hyperuricemia prior to gout were included. A questionnaire was used to determine whether participants had arthritis and the type of arthritis. Logistic regression was used to investigate the association between hyperuricemia and arthritis.

Result

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA) increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30). Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69), but the association was muted after adjusting demographic, socioeconomic factors, etc. For participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99) and the relationship remained after adjusting for education level, income to poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

Conclusion

Our data identified AH as the risk factor for incident arthritis, especially for OA, which might be exaggerated in aged population and female population.

Keywords: Arthritis, Asymptomatic hyperuricemia, Association, Risk

What is already known about this subject

- Hyperuricemia is a requisite risk factor for developing gouty arthritis, and research suggests that there may be some connection between hyperuricemia and other forms of arthritis as well.

What does this study add

- This study establishes a link between AH and arthritis, particularly with regards to OA, which becomes more pronounced with advancing age.

How might this impact on clinical practice

- The intimate relationship between hyperuricemia and OA may re-purpose FDA-approved urate-lowering therapy drugs in the treatment of OA.

Introduction

More than one in five adults in the United States had doctor-diagnosed arthritis, and arthritis-attributable activity limitations significantly increased over time independent of the population ageing[1]. By 2040, the adults with doctor-diagnosed arthritis are projected to increase 49% to 78.4 million (1 in 4 US adults), and the arthritis-attributable activity limitation will increase 52% to 34.6 million (1 in 9 adults)[2]. High medical care expenditures and earnings losses attributable to arthritis signaling the need for identification of disease and risk factor that are most need of interventions[3]. Osteoarthritis (OA), as the most comm form of arthritis, involves structural changes in the articular cartilage, subchondral bones, ligaments, bursae, synovium, and muscles surrounding the joint[4]. From 1990 to 2019, the global age standardized incidence rate of OA increased from 474 to 492 per 100, 000 population and expected to increase due to global population ageing[5, 6]. The link between metabolism and arthritis and the effect of interplay between immunological and metabolic processes is getting increasing attention as metabolic syndrome is implicated in a variety of arthritis, including OA[7, 8].

In 2007-2016, the prevalence of hyperuricemia, gout, and the urate-lowering therapy among patients with gout remained stable[9]. The true importance of asymptomatic hyperuricemia (AH) as a risk factor for incident gout as only half of patients with longstanding hyperuricemia develop clinically evident gout over 15 years[10, 11]. Advanced imaging, including ultrasonography or dual-energy CT, demonstrated

approximately 15–40% of patients with chronic hyperuricemia have silent monosodium urate crystal deposition[12]. As crystallization of monosodium urate is the turning point of hyperuricemia progress towards gout, whether hyperuricemia contribute to other arthritis remain uncertain[13].

Hyperuricemia and OA separately driven by common risk factors such as obesity and aging, intraarticular urate result in urate crystallization and deposition on the cartilage, disruption of cartilage by promotes urate crystallization and deposition[14]. The predilection for both OA and gout occur in the same joints strongly suggest that OA may predispose to the localized deposition of monosodium urate crystals, which influence structural joint damage[15-17]. Monosodium urate crystals have been shown to inhibit the viability and function of human chondrocytes in vitro with a dose-dependent manner[18]. Death of chondrocytes can lead to an increase in urate, which may even promote crystal deposition on the cartilage, further aggravating OA progression[14]. Monosodium urate crystals inhibit osteocyte viability and, through interactions with macrophages, indirectly promote a shift in osteocyte function that favors bone resorption and inflammation[19]. Uric acid is a danger signal of increasing risk OA through inflammasome activation[20]. Therefore, we hypothesized that hyperuricemia prior to gout was associated with OA. The aim of this study was to i) ascertain the association between AH and arthritis, ii) determine the association between AH and OA, iii) investigate the effect of age and gender on such association.

Patients and methods

Study population

NHANES is an ongoing longitudinal survey conducted by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the United States through a series of interviews and examination items. The NHANES is conducted biennially in a nationally representative, non-institutionalized civilian population, and use a hierarchical multi-stage probabilistic clustering design to select a representative sample of over-sampled participants. The sampling methods and examination information used in this study have been described in detail elsewhere[21]. NHANES was reviewed and approved by the NCHS Research Ethics Committee. All manipulations of the NHANES were carried out in accordance with the principles of the Helsinki Declaration. Written

informed consent was obtained from all participants in NHANES.

The study used data from NHANES database for the 2007-2018 study cycle (n=59,842) and excluded those who did not participate in the examination (n=2,428).We excluded participants who refused and don't know ever had or hadn't arthritis, refused to answer which type of arthritis (n=80), who are younger than 20 years old (n=24,002), who have missing and incomplete BMI, uric value, and smoking record (n=6,799). We also excluded participants who were told that you had gout(n=1,438) and participants with missing or incomplete low-density lipoprotein (LDL), cholesterol, and creatinine record. In the end, this study consisted of 13, 647 eligible participants (Figure 1), which is representative of the population size of 87,901,487.

Conditions of arthritis

The status of arthritis was classified using questionnaires. Participants aged 20 years and older were asked "Has a doctor or other health professional ever said that you had arthritis?". If the participants gave a positive answer, they were further asked "Which type of arthritis was it?". Participants' responses included rheumatoid arthritis (RA), OA, other, do not know type, and refuse to answer. Individuals were excluded from the current analysis if their self-reported type of arthritis declined to answer. A consistent relationship between self-reports of arthritis and a clinical diagnosis of arthritis has been demonstrated in previous reports[22].

Hyperuricemia

Hyperuricemia is an elevated level of uric acid in the blood. The normal upper limit for serum uric acid (SUA) at physiological levels is 6.8 mg/dL. This is the saturation point at which urate may precipitate under physiological conditions[23]. We put SUA>6.8 mg/dL was defined as hyperuricemia, and SUA≤6.8 mg/dL is defined as the normal state.

Covariates

Covariates are identified in statistical models by means of interview responses and examinations. Covariates were selected based on the results of interviews and examinations in the NHANES database to screen for factors that may be associated with OA risk and/or may be associated with AH, which could confound the association between OA and AH. Based on self-reported demographic characteristics, including gender, age, race/, education level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level

(PAL), diabetes.

Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race/ is divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other races. Education is grouped as high school or below, some college and college graduate or above. BMI is calculated from measured weight and height determined by standard NHANES protocols[24]. BMI is categorized as three groups: Normal (<18.5kg/m^2), Overweight (18.5–24.9kg/m^2) and Obesity (≥25 kg/m^2). Participants with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg are defined as hypertension[25]. PIR as a socioeconomic indicator are stratified into three levels: Low income (PIR < 1.3), Middle income (1.3 ≤ PIR < 3.5) and High income (PIR≥ 3.5).

Smoking status is categorized according to interview results as current (smoked more than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which includes moderate work activity, walking or cycling, moderate recreational activity, and vigorous activity, which includes vigorous work activity and vigorous recreational activity. Participants with self-reported diabetes had either a diabetes physician's diagnosis of diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance (OGTT), or/and HbA1c≥6.5%. Laboratory data included cholesterol, LDL, High-density lipoprotein (HDL), triglycerides, creatinine, and albumin.

Statistical analysis

Design factors involving complex weighting, clustering, and stratification in the NHANES database. Statistical analysis was conducted using STATA (version 16). Complex stratification designs were considered using appropriate sample weights in accordance with NHANES analytical reporting guidelines. In baseline study characteristics, means and standard errors (SEs) were used for continuous variables. Categorical variables were expressed as numbers and percentages. Chi-square test and t-test were used for categorical and continuous variables, respectively. A weighted logistic regression was used to assess the association between OA and AH and to control for confounding factors. Finally, subgroup analysis was performed using hierarchical multivariate regression. The 95% confidence intervals and p-values were calculated. A two-tailed test with p-values less

than 0.05 are considered significant.

Results

The characteristics of study participants

A total of 13,647 participants were eligible and included in the analysis from 2007-2008 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81% (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09% (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69). Between 2007-2008 and 2017-2018, the proportion of high school or below decreased, which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06, 33.00) to 30.47% (95%CI: 24.72, 36.23) .

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while the proportion of those who don't know arthritis decreased from 10.13% (95%CI: 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed a clear upward trend during the 12 years, from 8.70% (95%CI: 6.56, 10.85) in 2007-2008 to 12.44% (95%CI: 9.32, 15.55) in 2017-2018 ($p<0.01$).

In all age groups, the highest proportion of individuals with AH was observed in the 50-59 age group. (19.39% [95%CI: 17.17, 21.61]). A larger proportion of males (77.17% [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI: 20.63, 25.04]) (Table 2). There are significant differences in race between participants with and without AH ($p<0.01$). Participants in the AH group had higher levels of obesity, hypertension, diabetes, LDL, triglycerides, and creatinine than those in the healthy control group.

The prevalence of patients with osteoarthritic and AH (11.40% [95%CI: 9.56, 13.24]) is considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56, 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and don’t know: 7.54% (95%CI: 6.03, 9.05)) ($p<0.01$).

The characteristics of hyperuricemia and arthritis

Participants with arthritis, including OA, RA, other and don't know of arthritis, were more frequent in people aged over 50 years than those without arthritis (Table 1). The characteristics of the 13,647 participants included in our study with self-reported OA, RA, other, and don't know are presented using weighted statistics (Table 2). The prevalence of the four types of arthritis was higher among female participants than among male participants, which was most notable in OA (female: 65.94% vs male 30.06%).

213 **Table 1.** Baseline characteristics of arthritis group versus the non-arthritis group.

Characteristics	No Arthritis	OA	RA	Other	Don't konw	p value
N*	10089	1402	662	408	1086	
Gender						<0.01
Male	50.40(49.20,51.61)	34.06(31.15,36.97)	40.89(35.23,46.54)	40.90(34.65,47.15)	42.48(38.96,46.01)	
Female	49.60(48.39,50.80)	65.94(63.03,68.85)	59.11(53.46,64.77)	59.10(52.85,65.35)	57.52(53.99,61.04)	
Age						<0.01
20-29	24.10(22.69,25.52)	1.15(0.57,1.73)	2.62(0.30,4.94)	3.98(1.36,6.60)	3.17(1.79,4.55)	
30-39	21.40(20.16,22.64)	5.15(3.81,6.49)	6.11(3.79,8.43)	9.40(5.76,13.05)	6.35(4.47,8.24)	
40-49	20.74(19.35,22.14)	11.11(9.08,13.14)	15.63(11.52,19.73)	22.38(17.09,27.67)	15.00(11.89,18.10)	
50-59	16.53(15.39,17.66)	25.56(22.65,28.48)	26.90(20.60,33.20)	29.34(23.07,35.60)	27.60(23.49,31.71)	
60-69	10.22(9.19,11.25)	29.91(26.73,33.09)	24.48(19.59,29.36)	21.26(14.97,27.56)	23.61(20.04,27.19)	
70+	7.01(6.40,7.61)	27.11(24.11,30.12)	24.26(20.40,28.12)	13.64(9.48,17.79)	24.27(21.09,27.45)	
Race						<0.01
Other Races	18.98(17.18,20.77)	8.68(6.70,10.65)	15.21(10.33,20.09)	7.59(4.42,10.75)	11.13(8.86,13.39)	
Hispanic	6.83(5.62,8.05)	3.21(2.36,4.06)	5.11(3.68,6.54)	4.82(2.82,6.81)	5.14(3.69,6.59)	
Non-Hispanic White	63.36(60.50,66.21)	82.00(79.15,84.86)	63.62（57.67,69.57）	78.92（73.97,83.87）	72.33（68.49,76.18）	
Non-Hispanic Black	10.83(9.39,12.27)	6.11(4.65,7.57)	16.06(12.29,19.83)	8.67(5.89,11.46)	11.40(9.14,13.65)	
Education Level						<0.01
High school or below	37.86(35.61,40.10)	34.05(30.26,37.84)	52.13(45.41,58.85)	44.35(38.06,50.64)	50.09(45.46,54.73)	
Some College	29.76(28.19,31.34)	34.45(31.27,37.18)	32.25(27.08,37.42)	31.04(24.03,38.06)	31.61(27.66,35.57)	
College graduate or above	32.38(30.03,34.73)	31.50(27.68,35.33)	15.62(9.94,21.30)	24.61(17.82,31.39)	18.29(14.06,22.52)	
BMI						<0.01
Normal	33.47(31.83,35.12)	22.68(19.75,25.60)	27.88(22.90,32.85)	21.88(16.37,27.40)	20.66(17.17,24.15)	
Overweight	33.79(32.56,35.03)	32.36(28.93,35.80)	28.46(23.46,33.46)	29.37(23.76,34.98)	31.40(27.98,34.83)	
Obesity	32.74(31.13,34.35)	44.96(41.35,48.57)	43.66(38.74,48.58)	48.75(42.23,55.26)	47.93(43.56,52.31)	

Blood pressure						<0.01
Hypertension	36.92(35.28,38.56)	66.37(62.74,70.00)	63.74(57.17,70.31)	58.84(51.88,65.81)	63.77(59.68,67.86)	
Normal	63.08(61.44,64.72)	33.63(30.00,37.26)	36.26(29.69,42.83)	41.16(34.19,48.12)	36.23(32.14,40.32)	
PIR						<0.01
Low income	22.04(20.42,23.65)	16.37(13.61,19.13)	29.76(23.51,36.01)	22.45(16.84,28.06)	24.27(19.78,28.76)	
Middle income	35.83(34.13,37.52)	36.00(32.49,39.50)	36.22(30.28,42.16)	37.89(30.75,45.02)	36.74(32.08,41.40)	
Elevated income	42.14(39.89,44.38)	47.63(43.03,52.24)	34.02(27.68,40.36)	39.66(31.66,47.67)	38.98(32.91,45.05)	
Smoking						<0.01
Current	18.69(17.41,19.97)	18.21(15.47,20.95)	27.50(22.36,32.63)	27.31(21.50,33.12)	20.56(17.17,23.95)	
Before	21.77(20.30,23.24)	32.89(29.41,36.36)	33.14(26.79,39.49)	29.07(23.55,34.59)	34.03(30.01,38.05)	
Never	59.54(57.76,61.32)	48.90(45.48,52.32)	39.36(33.15,45.58)	43.62(37.28,49.96)	45.41(41.18,49.65)	
PAL						<0.01
Moderate activities	54.56(53.24,55.88)	73.88(70.67,77.08)	72.08(66.44,77.72)	67.01(59.61,74.40)	73.28(68.99,77.58)	
Vigorous activities	45.44(44.12,46.76)	26.12(22.92,29.33)	27.92(22.28,33.56)	32.99(25.60,40.39)	26.72(22.42,31.01)	
Diabetes						<0.01
Yes	8.50 (7.63,9.36)	15.81(13.36,18.27)	22.68(19.11,26.24)	16.27(10.90,21.63)	18.40(15.33,21.48)	
No	91.51(90.64,92.37)	84.19(81.73,86.64)	77.32(73.76,80.89)	83.73(78.37,89.10)	81.60(78.52,84.67)	
Uric acid						<0.01
AH	84.35(83.33,85.38)	84.18(81.78,86.59)	80.11(75.97,84.25)	84.42(79.68,89.17)	82.04(78.71,85.36)	
Healthy control	15.65(14.62,16.67)	15.82(13.41,18.22)	19.88(15.75,24.03)	15.58(10.83,20.32)	17.96(14.64,21.29)	
Cholesterol(mg/dl) †	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
LDL (mg/dl) †	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
HDL (mg/dl) †	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
Triglycerides(mg/dl) †	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
Creatinine(mg/dl) †	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
Albumin(mg/L) †	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout);

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Table 2. Baseline characteristics of high uric acid group versus the healthy control group.

Characteristics	Healthy control	AH	p value
N*	11387	2260	
Gender			<0.01
Male	41.66(40.55,42.76)	77.17(74.96,79.37)	
Female	58.34(57.24,59.45)	22.83(20.63,25.04)	
Age			<0.01
20-29	18.86(17.56,20.15)	17.30(15.07,19.53)	
30-39	18.03(16.98,19.07)	15.15(12.83,17.48)	
40-49	19.44(18.21,20.67)	17.39(14.72,20.05)	
50-59	19.05(17.98,20.12)	19.39(17.17,21.61)	
60-69	14.01(12.95,15.07)	15.66(13.36,17.95)	
70+	10.62(9.91,11.32)	15.11(13.21,17.00)	
Race			<0.01
Other Races	17.22(15.50,18.93)	14.33(12.20,16.47)	
Hispanic	6.32(5.21,7.44)	5.39(4.02 ,6.76)	
Non-Hispanic White	66.30(63.54,69.05)	68. 32(64.74,71.91)	
Non-Hispanic Black	10.16(8.80,11.53)	11.96(9.82,14.09)	
Education Level			0.137
High school or below	38.72(36.58,40.86)	40.33(37.04,43.63)	
Some College	30.44(28.96,31.92)	31.18(28.20,34.17)	
College graduate or above	30.84(28.51,33.16)	28.49(25.66,31.31)	
BMI			<0.01
Normal	34.09(32.60,35.58)	13.41(11.57,15.25)	
Overweight	33.07(32.07,34.08)	33.41(30.59,36.23)	
Obesity	32.83(31.48,34.19)	53.18(49.93,56.43)	
Blood pressure			<0.01
Hypertension	40.84(39.20,42.49)	59.45(56.85,62.06)	
Normal	59.16(57.51,60.80)	40.55(37.94,43.15)	
PIR			0.03
Low income	22.36(20.66,24.06)	18.98(17.00,20.97)	
Middle income	35.84(34.22,37.47)	36.73(33.94,39.53)	

Elevated income	41.79(39.48,44.11)	44.28(40.87,47.69)	
Smoking			<0.01
Current	19.72(18.32,21.11)	17.51(15.41,19.62)	
Before	23.23(21.86,24.60)	31.37(28.28,34.47)	
Never	57.06(55.32,58.79)	51.11(48.07,54.16)	
PAL			0.744
Moderate activities	59.26(57.72,60.81)	58.20(55.43,60.97)	
Vigorous activities	40.74(39.19,42.28)	41.80(39.03,44.57)	
Diabetes			<0.01
Yes	9.85(8.99,10.70)	15.68(14.06,17.30)	
No	90.15(89.30,91.01)	84.32(82.70,85.94)	
Arthritis			<0.01
No arthritis	75.13(73.67,76.59)	73.29(70.69,75.89)	
OA	11.54(10.55,12.53)	11.40(9.56,13.24)	
RA	3.54(3.11,3.97)	4.62(3.56,5.69)	
Other	3.24(2.69,3.79)	3.14(2.12,4.17)	
Dont know	6.55(5.88,7.22)	7.54(6.03,9.05)	
Cholesterol(mg/dl) †	191.01±40.22	192.23±41.65	0.1924
LDL (mg/dl)†	113.39±35.07	115.48±36.82	0.0088
HDL (mg/dl)†	55.58±15.89	48.87±15.10	<0.01
Triglycerides(mg/dl) †	110.45±62.12	139.39±73.24	<0.01
Creatinine(mg/dl)†	122.00±75.58	144.47±82.80	<0.01
Albumin(mg/dl)†	35.52±320.96	97.29±565.77	<0.01

BMI: body mass index; PIR: poverty income ratio; PA: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout).

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Participants with OA are higher in non-Hispanic white (82.00% [95%CI: 79.15, 84.86]), hypertension (66.37% [62.74, 70.00]), elevated income (47.63% [43.03, 52.24]), moderate activities (73.88% [70.67, 77.08]), cholesterol (194.85±42.44) and HDL (57.40±36.73) than those without arthritis. Similar trends are observed in participants with RA, OA, other types of arthritis and those who responded with "don't know" when asked about the type of arthritis.

And the proportion of participants who self-reported OA was the highest in arthritis. The proportion of AH is higher in participants with OA (84.18% [95%CI: 81.78, 85.59]) than in those with RA (80.11% [95%CI: 75.97, 84.25]) and don't know (82.04% [95%CI: 78.71, 85.36]) arthritis types. But it is slightly lower than no arthritis (84.35% [95%CI: 83.33, 85.38]) and other arthritis (84.42% [95%CI; 79.68,89.17]) ($p<0.01$) (Table 1)

The association between AH and arthritis

Overall, AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07, 1.69) (Table 3). However, the association muted in different models after adjusting for demographic, socioeconomic factors, etc.

Table 3. Association between asymptomatic hyperuricemia and total arthritis.

	Unadjusted model	model 1	model 2	model 3
Control (Reference)	1	1	1	1
Osteoarthritis				
OR (95% CI)	1.34(1.07,1.69)	1.14(0.87,1.49)	1.11(0.83,1.48)	1.07(0.80,1.41)
P	0.012	<0.01	<0.01	<0.01

Model1: Adjusted for age, gender, and race.

Model2: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, diabetes, hypertension and smoking record.

Model3: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine, and albumin.

For participants aged 40-49 years, AH is significantly associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99). The association remained after adjusted for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36) (Table 4).

Table 4. Subgroup analyses stratified by gender, age and race

	Model 1 (OR,95%, P)	Model 2(OR,95%, P)	Model 3(OR,95%,P)
Gander			
Male	1	1	1
Female	0.753(0.633,0.896)0.002	0.730 (0.608,0.877) 0.001	0.712(0.582,0.872)0.001
Age			
20-29	1	1	1
30-39	1.788(1.078,2.966)0.025	1.718(1.003,2.940)0.048	1.181(0.635,2.199)0.595
40-49	1.957(1.285,2.981)0.002	2.002(1.941,3.358)0.009	1.324(0.721,2.432)0.362
50-59	1.409(0.989,2.008)0.057	1.472(0.963,2.251)0.074	0.975(0.582,1.632)0.932
60-69	1.034(0.718,1.489)0.856	1.076(0.700,1.653)0.737	0.721(0.436,1.192)0.200
70+	1.106(0.789,1.549)0.556	1.122(0.725,1.737)0.602	0.739(0.426,1.282)0.278
Race			
Other Race	1	1	1
Hispanic	1.604(1.136,2.264)0.008	1.582(1.056,2.371)0.027	1.456(0.962,2.203)0.075
Non-Hispanic White	0.895(0.696,1.150)0.381	1.040(0.786,1.376)0.780	0.971(0.732,1.288)0.839
Non-Hispanic Black	2.017(1.471,2.765)0.000	2.305(1.622,3.276)0.000	2.203(1.536,3.160)0.000

Model1: Adjusted for age, gender, and race.

Model 2: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking record.

Model 3: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine and albumin.

For participants in non-Hispanic blacks, AH was significantly associated with new development of arthritis (OR=2.02, 95%CI: 1.47, 2.77). The results kept significant adjusting for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.31, 95%CI: 1.62, 3.28) and for cholesterol, LDL, HDL, triglyceride, creatinine, and albumin (OR=2.20,95%CI: 1.55, 3.16) (Table 4).

Compared with male participants, female participants with AH are more likely to develop OA (OR=1.35, 95%CI: 1.14, 1.60), RA (OR: 1.08 95%CI: 0.83, 1.41), other arthritis (OR: 1.00, 95%CI 0.78,1.29), Don't know (OR: 0.99, 95%CI: 0.82,1.20). This

phenomenon is more obvious in the OA subgroup. (sTable 2). Among participants aged > 50 years, there is a significant association between AH and different types of arthritis (including OA, RA, other, don't know). More importantly, the strength of this association increased with age, specifically for 50-59 year, 60-69 years, 70+ years.

Discussion

Based on 12 years of nationally representative data from NHANES, our data showed a relationship between AH and incident arthritis, especially OA. About 20% of the general population affected by hyperuricemia, which might be more prominent in male and aged population[26]. In 2010-2012, US had doctor-diagnosed arthritis and arthritis-attributable activity limitation was 52.5 million and 22.7 million are projected to increase 49% and 52% to 78.4 million and 34.6 million by 2040, respectively[2].

Although hyperuricemia is a major contributor to the development of gouty arthritis, accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic arthritis and spondylarthritis. In vitro studies on synoviocytes from healthy and rheumatoid arthritis subjects revealed that monosodium urate crystals could increase the release of the inflammatory cytokine IL-6, the chemokine CXCL8 and the matrix metalloproteinase-1[27]. The injection of urate crystals in vivo leads to produce main mediators in the pathogenesis of PsA, such as IL-17 [28]. The hyperuricemia not only play an important role the development and progression of psoriatic arthritis, but also affect severity of clinical manifestations and degree of inflammation[29]. Monosodium urate crystals interact with articular tissues to influence the development of axial spondyloarthritis as monosodium urate crystal deposition associated with the progress of radiographic grade at the sacroiliac joint[16, 30].

Our data confirm the AH is danger signal of increasing risk for OA[20]. An increasing body of evidence suggests that AH, characterized by elevated serum uric acid levels without any symptoms of gout or kidney stone disease, may be associated with an increased risk of OA, particularly in weight-bearing joints such as the knee[14, 31, 32]. The relationship between AH and arthritis is complex and multifaceted, and the exact nature of this relationship is not yet clear. Hyperuricemia may promote the development of arthritis via deposition of urate crystals in the joints, promoting chronic low-grade inflammation, and exacerbating oxidative stress[18, 20, 33]. However, it is also possible that the

association between hyperuricemia and arthritis is partially due to common risk factors such as obesity and metabolic syndrome[34, 35]. Further research is needed to better understand the relationship between these two conditions and to identify potential therapeutic targets for the prevention or treatment of arthritis in patients with hyperuricemia.

The intimate relationship between hyperuricemia and OA may re-purpose FDA-approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opioids[36]. However, these drugs could only used to relieve the clinical symptoms but not decrease the onset of arthritis. In recent years, there has been growing interest in exploring the role of urate-lowering therapy in the treatment of OA[37]. Urate crystal deposition can directly damage cartilage, stimulate the production of pro-inflammatory cytokines, and lead to inflammation and cartilage degradation[38]. Urate-lowering therapy drugs such as allopurinol and febuxostat have been shown to have anti-inflammatory properties, inhibit the production of reactive oxygen species, reduce the expression of pro-inflammatory cytokine[39-41]. Our results also suggest pharmacological treatment of AH via a treat-to-target (T2T) strategy may decrease incident of arthritis, especially for OA. The T2T strategy involves targeting specific uric acid levels and adjusting drug therapy accordingly to achieve this goal[42, 43].

Our findings highlight those female participants with AH are more likely to develop arthritis, especially for OA, than male participants, and ageing may exaggerate this trend. Among adults in the US, mean serum urate levels were 6.0 mg/dl in men and 4.8 mg/dl in women, and hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[9]. Studies have also shown that hyperuricemia is more common in men over 30 and women over 50[44]. The gender and age associated increase in serum uric acid levels may be explained by menopause in women and alcohol consumption in men[45]. Menopause can lead to an increase in serum uric acid levels, while postmenopausal hormone replacement therapy may be associated with a decrease in serum uric acid levels[46]. The difference in serum uric acid levels between men and women is due to the increased renal uric acid clearance caused by estrogen in women before menopause[47]. When osteophytes were present, blood uric acid levels were significantly elevated in women with OA, but this was

not observed in men with OA[48]. Female typically have a higher prevalence of hand and knee arthritis than males, females also tend to have more severe knee OA, particularly after menopausal age[49].

The strength of our study was the use of data from a large, nationally representative sample. However, results should be interpreted with caution with inherent limitation. First, it is not possible to interpret the findings from a causal point of view due to the cross-sectional approach. Prospective study and mendelian randomization study are needed to further investigate the relationship between the AH and arthritis, especially OA. Second, recall bias may affect the accuracy of prevalence estimates although this study used CDC-recommended self-reported and physician-diagnosed arthritis as case definitions[22, 50]. Third, our result might be charged with choosing a single number to represent prevalent of arthritis in the US population as it only included adults in the national non-institutionalized population of the country[51]. Fourth, medication use for the participants was not included in this study. Finally, we had limited information on the involvement of OA in each participant, such as imaging and treatment procedures.

In summary, our study results suggest that AH patients may benefit from close monitoring for the development of arthritis, understanding the relationship between hyperuricemia and arthritis, and identifying factors that contribute to their increased risk of these diseases, which may be of great significance for the prevention and management of these conditions.

Contributors

Prof. JRG is the guarantor of the study and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Zhenguo Liang, Dr. Dongze Wu, and Prof. Jieruo Gu, conceived and designed the study, performed the analysis, and wrote the paper. All authors read and commented on the manuscript and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclaimer

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Declaration of interests

The authors declare no conflict of interests.

Ethical approval

The data released from the National Health and Nutrition Examination Survey did not require informed patient consent. This study used an anonymized publicly available data set with no identifiable information on the survey participants, and thus did not require ethics approval.

Data sharing

The data used for the analyses are publicly available from the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC) in the United States (https://www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

Supplemental appendix

sTable 1. Characteristics of participants included in this study.

sTable 2. Subgroup analysis of the association of arthritis subtype (RA, OA, others and don't know) and AH.

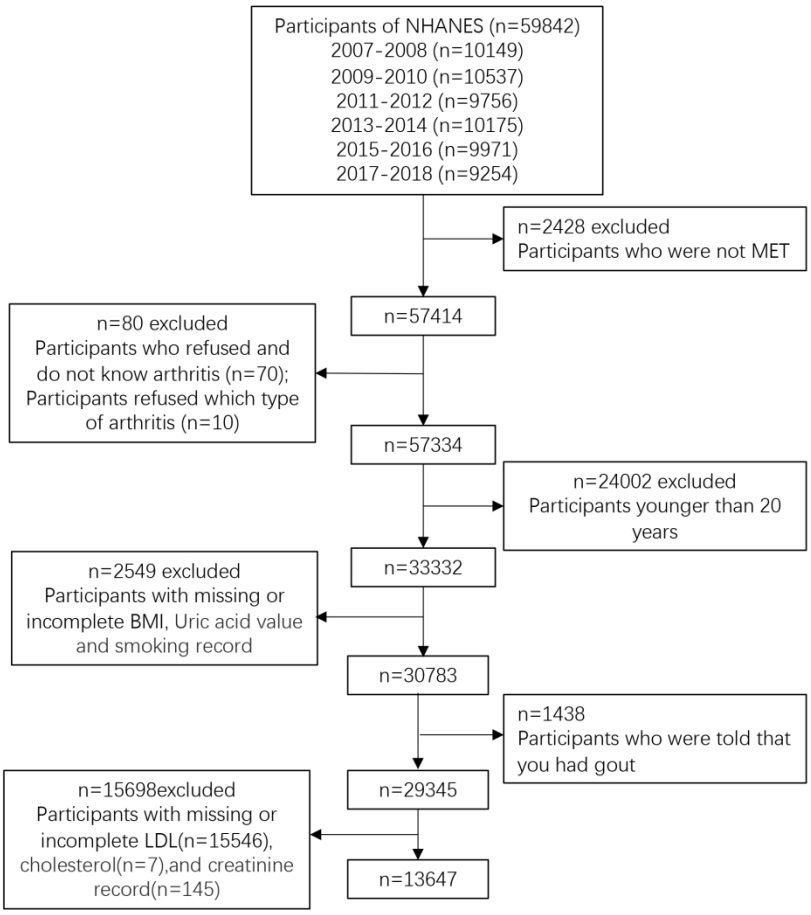

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

188x175mm (300 x 300 DPI)

Supplementary materials

The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

Supplementary Tables

sTable1. Characteristics of participants included in this study

sTable2. Subgroup analysis of the association of arthritis subtype (RA, OA, others and don't know) and AH.

Supplementary Table 1. Characteristics of participants included in this study

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	p
N*	2330	2528	2229	2367	2067	2126	
Uricacid							0.438
NA	83.65(81.60,85.69)	84.50(82.38,86.62)	84.71(82.87,86.64)	83.55(81.95,85.15)	84.13(82.09,86.17)	83.61(80.70,86.53)	
AH	16.35(14.01,18.40)	15.50(13.38,17.62)	15.29(13.46,17.13)	16.45(14.85,18.05)	15.87(13.83,17.91)	16.39(13.47,19.30)	
Gender							0.279
Male	47.25(45.60,48.89)	45.56(43.56,47.55)	47.90(45.04,50.75)	47.69(45.61,49.77)	47.36(45.31,49.42)	48.09(44.95,51.22)	
Female	52.75(51.11,54.40)	54.44(52.45,56.44)	52.10(49.25,54.96)	52.31(50.23,54.39)	52.64(50.58,54.69)	51.91(48.78,55.05)	
Age							<0.01
20-29	19.13(16.42,21.85)	19.35(16.80,21.90)	18.23(15.01,21.45)	18.40(15.73,21.08)	16.67(14.61,18.72)	19.86(16.81,22.90)	
30-39	18.20(15.96,20.43)	16.98(14.62,19.35)	18.53(15.67,21.39)	17.24(15.16,19.31)	15.59(14.04,17.15)	18.76(15.92,21.60)	
40-49	20.97(17.50,24.44)	21.50(19.52,23.49)	18.86(15.20,22.52)	19.43(16.80,22.07)	18.56(15.67,21.45)	15.71(13.13,18.28)	
50-59	19.29(16.77,21.80)	19.37(16.98,21.77)	19.08(17.07,21.08)	18.17(15.58,20.76)	18.81(17.09,20.54)	19.93(16.84,23.02)	
60-69	11.44(9.42,13.46)	11.18(9.90,12.46)	14.03(12.10,15.96)	14.71(12.03,17.38)	19.21(16.43,22.00)	14.81(11.45,18.16)	
70+	10.98(9.65,12.30)	11.60(10.10,13.10)	11.26(9.65,12.88)	12.05(10.37,13.73)	11.16(9.36,12.96)	10.95(8.93,12.97)	
Race/Ethnicity							<0.01
Other Race	13.87(10.43,17.31)	16.55(11.72,21.38)	15.80(11.44,20.16)	16.88(12.75,21.02)	17.24(13.58,20.90)	19.91(16.40,23.42)	
Hispanic	5.09(2.60,7.58)	5.84(2.94,8.74)	6.74(3.84,9.64)	5.67(2.34,8.61)	6.74(3.88,9.59)	6.86(5.00,8.72)	
Non-Hispanic White	70.37(63.63,77.11)	66.91(60.23,73.59)	68.04(61.22,74.87)	67.07(60.01,74.13)	65.74(57.81,73.66)	61.96(57.22,66.69)	

Non-Hispanic Black	10.67(6.63,14.70)	10.70(8.67,12.72)	9.42(5.94,12.90)	10.37(7.68,13.07)	10.29(5.86,14.71)	11.27(7.61,14.93)	
Education Level							<0.01
High school or below	43.02(37.88,48.16)	41.31(37.13,45.52)	37.42(31.97,42.87)	36.42(30.79,42.04)	36.46(30.23,42.68)	39.61(36.03,43.19)	
Some college	28.45(26.32,30.58)	29.63(26.71,32.56)	31.10(27.90,34.30)	32.90(29.91,35.90)	31.18(27.20,35.16)	29.91(25.07,34.76)	
College graduate or above	28.53(24.06,33.00)	29.05(25.76,32.33)	31.48(25.02,37.94)	30.68(26.29,35.07)	32.36(25.35,39.37)	30.47(24.72,36.23)	
BMI							<0.01
Normal	33.39(31.60,35.19)	32.13(28.74,35.52)	31.68(27.63,35.73)	31.24(28.78,33.70)	27.17(23.38,30.96)	29.29(25.52,33.05)	
Overweight	35.11(32.97,37.26)	32.96(30.44,35.48)	33.36(31.12,35.60)	33.31(30.91,35.70)	32.66(31.03,34.28)	31.53(29.18,33.8)	
Obesity	31.49(28.61,34.37)	34.91(32.02,37.79)	34.96(31.50,38.42)	35.45(33.20,37.70)	40.17(36.34,44.00)	39.18(35.37,43.00)	
Blood pressure							<0.01
Hypertension	40.92(37.47,44.37)	40.38(36.47,44.30)	45.82(41.97,49.68)	43.84(39.24,48.43)	44.44(40.49,48.40)	46.99(43.71,50.28)	
Normal	59.08(55.63,62.53)	59.62(55.70,63.53)	54.18(50.32,58.03)	56.16(51.57,60.76)	55.56(51.60,59.51)	53.01(49.72,56.29)	
PIR							<0.01
Low income	19.38(16.16,22.61)	21.90(19.24,24.56)	24.29(20.21,28.38)	25.33(19.07,31.59)	19.64(16.45,22.82)	20.01(17.46,22.56)	
Middle income	33.99(30.47,37.52)	37.50(33.75,41.26)	35.70(31.24,40.17)	33.69(30.70,36.68)	37.50(34.14,40.87)	37.61(33.36,41.86)	
High income	46.62(41.80,51.44)	40.60(36.83,44.36)	40.00(33.29,46.72)	40.98(34.20,47.76)	42.86(37.83,47.88)	42.38(37.89,46.88)	
Somking							0.01
Current	21.61(18.39,24.83)	18.98(17.51,20.45)	20.06(16.75,23.36)	19.50(15.86,23.14)	18.73(15.50,21.97)	17.47(14.68,20.27)	
Before	24.99(22.25,27.73)	24.21(20.55,27.87)	23.04(20.16,25.92)	23.68(20.64,26.72)	26.46(22.62,30.31)	24.90(22.47,27.32)	
Never	53.40(49.73,57.07)	56.80(53.00,60.61)	56.90(53.76,60.05)	56.82(52.86,60.78)	54.81(50.57,59.04)	57.63(54.64,60.62)	

PAL							<0.01
Moderate activities	58.98(55.40,62.57)	62.32(59.17,65.48)	61.71(57.96,65.46)	62.05(59.40,64.70)	57.56(54.23,60.90)	52.20(49.94,54.47)	
Vigorous activities	41.02(37.43,44.60)	37.68(34.52,40.83)	38.29(34.54,42.04)	37.95(35.30,40.60)	42.44(39.10,45.77)	47.80(45.53,50.06)	
Diabetes							<0.01
Yes	10.17(8.32,12.03)	9.47(8.21,10.74)	10.20(8.31,12.09)	10.34(8.83,11.84)	12.25(9.95,14.55)	12.14(9.78,14.49)	
No	89.83(87.97,91.68)	90.53(89.26,91.79)	89.80(87.91,91.69)	89.66(88.16,91.17)	87.75(85.45,90.05)	87.86(85.51,90.22)	
With or without arthritis							<0.01
No arthritis	74.05(70.64,77.47)	74.90(72.43,77.38)	77.19(73.85,80.53)	75.09(72.40,77.78)	73.16(70.09,76.24)	74.47(70.56,78.38)	
Arthritis	25.95(22.53,29.36)	25.10(22.62,27.57)	22.81(19.47,26.15)	24.91(22.22,27.60)	26.84(23.76,29.91)	25.53(21.62,29.44)	
OA	8.70(6.56,10.85)	9.56(8.30,10.82)	11.30(8.92,13.68)	13.88(11.87,15.89)	12.92(10.99,14.86)	12.44(9.32,15.55)	
RA	3.57(2.87,4.27)	4.11(3.18,5.04)	3.90(2.78,5.02)	3.09(2.15,4.02)	3.59(2.53,4.64)	4.04(2.82,5.25)	
Other	3.54(2.56,4.52)	3.64(2.80,4.47)	2.88(1.39,4.37)	2.98(2.05,3.91)	3.33(1.66,5.01)	3.04(1.78,4.30)	
Dont know	10.13(8.22,12.05)	7.79(6.41,9.17)	4.73(3.14,6.33)	4.96(4.03,5.89)	6.99(5.25,8.73)	6.02(4.66,7.37)	
Cholesterol(mg/dl)†	194.90±40.98	195.00±39.66	191.78±39.95	188.44±39.94	190.31±41.06	186.04±40.55	<0.01
LDL(mg/dl)†	115.60±35.83	116.32±34.82	114.41±34.74	111.74±35.10	112.89±35.82	110.72±35.69	<0.01
HDL(mg/dl)†	54.15±15.40	54.40±15.95	53.78±14.93	54.58±16.11	55.97±17.56	54.02±15.74	<0.01
Triglyceride(mg/dl)†	125.72±66.36	121.43±64.17	117.95±64.42	110.61±65.08	107.26±63.05	106.48±63.30	<0.01
Creatinine(mg/dl)†	123.56±74.93	124.01±74.60	125.83±78.25	119.58±74.02	126.23±77.54	136.33±83.94	<0.01
Albumin(mg/dl)†	58.18±663.81	33.09±182.80	37.78±211.82	40.30±250.06	51.49±338.92	56.01±379.49	0.105

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL with no gout); NA: no-hyperuricemia.

Supplementary Table 2. Subgroup analysis of the association of arthritis subtype (RA, OA, others and don't know) and AH

	OA (OR,95%, P)	RA (OR,95%, P)	Other (OR,95%, P)	Don't know (OR,95%, P)
Gander				
Male	1	1	1	1
Female	1.35(1.14,1.60)0.00	1.08(0.83,1.41)0.59	1.00(0.78,1.29)1.00	0.99(0.82,1.20)0.96
Age				
20-29	1	1	1	1
30-39	0.36(0.27,0.49)0.00	0.36(0.24,0.54)0.00	0.35(0.23,0.55)0.00	0.38(0.27,0.53)0.00
40-49	0.80(0.62,1.04)0.97	0.99(0.71,1.38)0.96	0.88(0.64,1.21)0.44	0.95(0.70,1.30)0.74
50-59	2.16(1.72,2.72)0.00	2.12(1.50,3.00)0.000	1.35(1.00,1.83)0.51	1.90(1.44,2.49)0.00
60-69	4.18(3.26,5.35)0.00	3.34(2.50,4.46)0.000	1.69(1.13,2.53)0.01	2.70(1.92,3.78)0.00
70+	5.50(4.18,7.22)0.00	4.57(3.40,6.15)0.000	1.51(0.99,2.33)0.06	4.24(3.16,5.69)0.00

RA: rheumatoid arthritis; OA: osteoarthritis; AH: asymptomatic hyperuricemia

All data were adjusted for gender, age, race, BMI, education level and poverty to income ratio, hypertension, ever cigarette smoking and diabetes.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

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The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

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Running Head: Association between asymptomatic hyperuricemia and risk of arthritis.

Abstract

Background

Arthritis is thought to be closely related to serum uric acid. The study aims to assess the association between asymptomatic hyperuricemia (AH) and arthritis.

Methods

A multistage, stratified cluster was used to conduct a cross-sectional study of adult U.S. civilians aged≥ 20 years from the 2007-2018 National Health and Nutrition Examination Survey (NHANES). Participants with hyperuricemia and without hyperuricemia prior to gout were included. A questionnaire was used to determine whether participants had arthritis and the type of arthritis. Logistic regression was used to investigate the association between hyperuricemia and arthritis.

Result

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA) increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30). Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69), but the association was muted after adjusting demographic, socioeconomic factors, etc. For participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99) and the relationship remained after adjusting for education level, income to poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

Conclusion

Our data identified AH as the risk factor for incident arthritis, especially for OA, which might be exaggerated in aged population and female population.

Keywords: Arthritis, Asymptomatic hyperuricemia, Association, Risk

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study marks the inaugural analysis of population characteristics among participants with arthritis in the NHANES database from 2007 to 2019. It delves into the specific characteristics of arthritis and asymptomatic hyperuricemia, as well as exploring the potential connections between these two conditions.
- Beyond its well-documented association with gout, this study lends credence to the notion that asymptomatic hyperuricemia may serve as a predictive factor for the onset of arthritis, with a particular emphasis on OA.
- While the data within the NHANES database has undergone significant refinement, it's important to note that the statistical cycle occurs biennially, and adjustments are made to the statistical scheme in different cycles.
- Our analysis focused exclusively on the NHANES database spanning the years 2007 to 2019. We did not extend our analysis to other time periods, which represents a limitation inherent to cross-sectional studies. It's important to recognize that the NHANES database, compiled by the CDC, encompasses data from the entire American population. Consequently, its applicability to other countries or ethnic groups worldwide may be constrained due to these specific demographics and contexts.

Introduction

More than one in five adults in the United States had doctor-diagnosed arthritis, and arthritis-attributable activity limitations significantly increased over time independent of the population ageing[1]. By 2040, the adults with doctor-diagnosed arthritis are projected to increase 49% to 78.4 million (1 in 4 US adults), and the arthritis-attributable activity limitation will increase 52% to 34.6 million (1 in 9 adults)[2]. High medical care expenditures and earnings losses attributable to arthritis signaling the need for identification of disease and risk factor that are in most need for interventions[3]. OA as the most common form of arthritis, involves structural changes in the articular cartilage, subchondral bones, ligaments, bursae, synovium, and muscles surrounding the joint[4]. From 1990 to 2019, the global age standardized incidence rate of OA increased from 474 to 492 per 100, 000 population and expected to increase due to global population ageing[5, 6]. About 20% of the general population affected by hyperuricemia, which might be more prominent in male and aged population[7]. Prior research has consistently shown a

significant correlation between arthritis, particularly OA and rheumatoid arthritis (RA), and hypertension[8]. The intricate relationship between metabolic processes and arthritis, alongside the interplay between metabolic and immunological factors, is garnering heightened attention. Metabolic syndrome's implication in various forms of arthritis, such as OA, is increasingly recognized. [9, 10].

In 2007-2016, the prevalence of hyperuricemia, gout, and the urate-lowering therapy among patients with gout remained stable[11]. The true significance of asymptomatic hyperuricemia (AH) as a risk factor for incident gout becomes apparent when considering that only half of patients with longstanding hyperuricemia develop clinically evident gout over a 15-year period.[12, 13]. Advanced imaging, including ultrasonography or dual-energy CT, demonstrated approximately 15–40% of patients with chronic hyperuricemia have silent monosodium urate crystal deposition[14]. As the crystallization of monosodium urate marks the progression of hyperuricemia towards gout, it remains uncertain whether hyperuricemia contributes to other forms of arthritis.[15].

Both hyperuricemia and OA are influenced by common risk factors such as obesity and aging. This shared relationship between risk factors suggests a potential connection between the hyperuricemia and OA, with intraarticular urate contributing to crystallization and cartilage disruption in the context of these shared risk factors.[16]. The predilection for both OA and gout occur in the same joints strongly suggest that OA may predispose to the localized deposition of monosodium urate crystals, which influence structural joint damage[17-19]. Monosodium urate crystals have been shown to inhibit the viability and function of human chondrocytes in vitro with a dose-dependent manner[20]. Death of chondrocytes can lead to an increase in urate, which may even promote crystal deposition on the cartilage, further aggravating OA progression[16]. Monosodium urate crystals inhibit osteocyte viability and, through interactions with macrophages, indirectly promote a shift in osteocyte function that favors bone resorption and inflammation[21]. Uric acid is a danger signal of increasing risk OA through inflammasome activation[22]. Therefore, we hypothesized that hyperuricemia prior to gout was associated with OA. The aim of this study was to i) ascertain the association between AH and arthritis, ii) determine the association between AH and OA, iii) investigate the effect of age and gender on such association.

Patients and methods

Patient and Public Involvement

NHANES is an ongoing longitudinal survey conducted by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the United States through a series of interviews and examination items. The NHANES is conducted biennially in a nationally representative, non-institutionalized civilian population, and use a hierarchical multi-stage probabilistic clustering design to select a representative sample of over-sampled participants. The sampling methods and examination information used in this study have been described in detail elsewhere[23]. NHANES was reviewed and approved by the NCHS Research Ethics Committee. All manipulations of the NHANES were carried out in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants in NHANES.

The study used data from NHANES database for the 2007-2018 study cycle (n=59,842) and excluded those who did not participate in the examination (n=2,428).We excluded participants who refused and don't know ever had or hadn't arthritis, refused to answer which type of arthritis (n=80), who are younger than 20 years old (n=24,002), who have missing and incomplete BMI, uric value, and smoking record (n=2,549). We also excluded participants who were told that you had gout(n=1,438) and participants with missing or incomplete low-density lipoprotein (LDL), cholesterol, and creatinine record. In the end, this study consisted of 13, 647 eligible participants (Figure 1), which is representative of the population size of 87,901,487.

Conditions of arthritis

The status of arthritis was classified using questionnaires. Participants aged 20 years and older were asked "Has a doctor or other health professional ever said that you had arthritis?". If the participants gave a positive answer, they were further asked "Which type of arthritis was it?". Participants' responses included RA, OA, other, do not know type, and refuse to answer. Individuals were excluded from the current analysis if their self-reported type of arthritis declined to answer. A consistent relationship between self-reports of arthritis and a clinical diagnosis of arthritis has been demonstrated in previous reports[24].

Hyperuricemia

Hyperuricemia is an elevated level of uric acid in the blood. The normal upper limit for

serum uric acid (SUA) at physiological levels is 6.8 mg/dL. This is the saturation point at which urate may precipitate under physiological conditions[25, 26]. We put SUA>6.8 mg/dL was defined as hyperuricemia, and SUA≤6.8 mg/dL is defined as the normal state.

Covariates

Covariates are identified in statistical models by means of interview responses and examinations. Covariates that could confound the association between OA and AH were selected based on the results of interviews and examinations in the NHANES database. These factors were chosen to screen for variables that might be associated with OA risk and/or could be associated with AH. This selection aimed to minimize potential confounding variables in the association between OA and AH. The chosen covariates included self-reported demographic characteristics, such as gender, age, race, education level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level (PAL), and diabetes.

Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race is divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other races. Education is grouped as high school or below, some college and college graduate or above. BMI is calculated from measured weight and height determined by standard NHANES protocols[27]. BMI is categorized as three groups: Normal (<18.5kg/m^2), Overweight (18.5–24.9kg/m^2) and Obesity (≥25 kg/m^2). Participants with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg are defined as hypertension[28]. PIR as a socioeconomic indicator is stratified into three levels: Low income (PIR < 1.3), Middle income (1.3 ≤ PIR < 3.5) and High income (PIR≥ 3.5).

Smoking status is categorized according to interview results as current (smoked more than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which includes moderate work activity, walking or cycling, moderate recreational activity, and vigorous activity, which includes vigorous work activity and vigorous recreational activity. Participants with self-reported diabetes had either a diabetes physician's diagnosis of diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance (OGTT), or/and HbA1c≥6.5%. Laboratory data included cholesterol, LDL, High-density

lipoprotein (HDL), triglycerides, creatinine, and albumin.

Statistical analysis

Design factors involving complex weighting, clustering, and stratification in the NHANES database. Statistical analysis was conducted using STATA (version 16). Complex stratification designs were considered using appropriate sample weights in accordance with NHANES analytical reporting guidelines. In baseline study characteristics, means and standard errors (SEs) were used for continuous variables. Categorical variables were expressed as numbers and percentages. Chi-square test and t-test were used for categorical and continuous variables, respectively. A weighted logistic regression was used to assess the association between OA and AH and to control for confounding factors. Finally, subgroup analysis was performed using hierarchical multivariate regression. The 95% confidence intervals and p-values were calculated. A two-tailed test with p-values less than 0.05 are considered significant.

Results

The characteristics of study participants

A total of 13,647 participants were eligible and included in the analysis from 2007-2008 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81% (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09% (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69). Between 2007-2008 and 2017-2018, the proportion of high school or below decreased, which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06, 33.00) to 30.47% (95%CI: 24.72, 36.23) (sTable 1).

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while the proportion of those who don't know arthritis decreased from 10.13% (95%CI: 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed

a clear upward trend during the 12 years, from 8.70% (95%CI: 6.56, 10.85) in 2007-2008 to 12.44% (95%CI: 9.32, 15.55) in 2017-2018 (p<0.01) (sTable 1).

The 50-59 age group displayed the highest percentage of individuals with AH (19.39% [95%CI: 17.17, 21.61]) among all the age groups that were examined. A larger proportion of males (77.17% [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI: 20.63, 25.04]) (Table 1). There are significant differences in race between participants with and without AH (p<0.01). Participants in the AH group had higher levels of obesity, hypertension, diabetes, LDL, triglycerides, and creatinine than those in the normal state group (Table 1).

The prevalence of patients with OA and AH (11.40% [95%CI: 9.56, 13.24]) is considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56, 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and unspecified: 7.54% (95%CI: 6.03, 9.05)) (p<0.01) (Table 1).

The characteristics of hyperuricemia and arthritis

The higher frequency of participants with arthritis, including OA, RA, other forms, and those who were unaware of having arthritis, among individuals aged over 50 years, suggests that age may be a contributing factor to the prevalence of arthritis in this population (Table 2). The characteristics of the 13,647 participants included in our study with self-reported OA, RA, other, and Unspecified are presented using weighted statistics (Table 1). The prevalence of the four types of arthritis was higher among female participants than among male participants, which was most notable in OA (female: 65.94% vs male 34.06%) (Table 2).

Table 1. Baseline characteristics of high uric acid group versus the normal state group.

Characteristics	Normal state	AH	p value
N*	11387	2260	
Gender			<0.01
Male	41.66(40.55,42.76)	77.17(74.96,79.37)	
Female	58.34(57.24,59.45)	22.83(20.63,25.04)	
Age			<0.01
20-29	18.86(17.56,20.15)	17.30(15.07,19.53)	
30-39	18.03(16.98,19.07)	15.15(12.83,17.48)	
40-49	19.44(18.21,20.67)	17.39(14.72,20.05)	
50-59	19.05(17.98,20.12)	19.39(17.17,21.61)	
60-69	14.01(12.95,15.07)	15.66(13.36,17.95)	
70+	10.62(9.91,11.32)	15.11(13.21,17.00)	
Race			<0.01
Other Races	17.22(15.50,18.93)	14.33(12.20,16.47)	
Hispanic	6.32(5.21,7.44)	5.39(4.02 ,6.76)	
Non-Hispanic White	66.30(63.54,69.05)	68. 32(64.74,71.91)	
Non-Hispanic Black	10.16(8.80,11.53)	11.96(9.82,14.09)	
Education Level			0.137
High school or below	38.72(36.58,40.86)	40.33(37.04,43.63)	
Some College	30.44(28.96,31.92)	31.18(28.20,34.17)	
College graduate or above	30.84(28.51,33.16)	28.49(25.66,31.31)	
BMI			<0.01
Normal	34.09(32.60,35.58)	13.41(11.57,15.25)	
Overweight	33.07(32.07,34.08)	33.41(30.59,36.23)	
Obesity	32.83(31.48,34.19)	53.18(49.93,56.43)	
Blood pressure			<0.01
Hypertension	40.84(39.20,42.49)	59.45(56.85,62.06)	
Normal	59.16(57.51,60.80)	40.55(37.94,43.15)	
PIR			0.03
Low income	22.36(20.66,24.06)	18.98(17.00,20.97)	
Middle income	35.84(34.22,37.47)	36.73(33.94,39.53)	

Elevated income	41.79(39.48,44.11)	44.28(40.87,47.69)	
Smoking			<0.01
Current	19.72(18.32,21.11)	17.51(15.41,19.62)	
Before	23.23(21.86,24.60)	31.37(28.28,34.47)	
Never	57.06(55.32,58.79)	51.11(48.07,54.16)	
PAL			0.744
Moderate activities	59.26(57.72,60.81)	58.20(55.43,60.97)	
Vigorous activities	40.74(39.19,42.28)	41.80(39.03,44.57)	
Diabetes			<0.01
Yes	9.85(8.99,10.70)	15.68(14.06,17.30)	
No	90.15(89.30,91.01)	84.32(82.70,85.94)	
Arthritis			<0.01
No arthritis	75.13(73.67,76.59)	73.29(70.69,75.89)	
OA	11.54(10.55,12.53)	11.40(9.56,13.24)	
RA	3.54(3.11,3.97)	4.62(3.56,5.69)	
Other	3.24(2.69,3.79)	3.14(2.12,4.17)	
Unspecified	6.55(5.88,7.22)	7.54(6.03,9.05)	
Cholesterol(mg/dl) †	191.01±40.22	192.23±41.65	0.1924
LDL (mg/dl)†	113.39±35.07	115.48±36.82	0.0088
HDL (mg/dl)†	55.58±15.89	48.87±15.10	<0.01
Triglycerides(mg/dl) †	110.45±62.12	139.39±73.24	<0.01
Creatinine(mg/dl)†	122.00±75.58	144.47±82.80	<0.01
Albumin(mg/dl)†	35.52±320.96	97.29±565.77	<0.01

BMI: body mass index; PIR: poverty income ratio; PA: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout).

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Table 2. Baseline characteristics of arthritis group versus the non-arthritis group.

Characteristics	No Arthritis	OA	RA	Other	Unspecified	p value
N*	10089	1402	662	408	1086	
Gender						<0.01
Male	50.40(49.20,51.61)	34.06(31.15,36.97)	40.89(35.23,46.54)	40.90(34.65,47.15)	42.48(38.96,46.01)	
Female	49.60(48.39,50.80)	65.94(63.03,68.85)	59.11(53.46,64.77)	59.10(52.85,65.35)	57.52(53.99,61.04)	
Age						<0.01
20-29	24.10(22.69,25.52)	1.15(0.57,1.73)	2.62(0.30,4.94)	3.98(1.36,6.60)	3.17(1.79,4.55)	
30-39	21.40(20.16,22.64)	5.15(3.81,6.49)	6.11(3.79,8.43)	9.40(5.76,13.05)	6.35(4.47,8.24)	
40-49	20.74(19.35,22.14)	11.11(9.08,13.14)	15.63(11.52,19.73)	22.38(17.09,27.67)	15.00(11.89,18.10)	
50-59	16.53(15.39,17.66)	25.56(22.65,28.48)	26.90(20.60,33.20)	29.34(23.07,35.60)	27.60(23.49,31.71)	
60-69	10.22(9.19,11.25)	29.91(26.73,33.09)	24.48(19.59,29.36)	21.26(14.97,27.56)	23.61(20.04,27.19)	
70+	7.01(6.40,7.61)	27.11(24.11,30.12)	24.26(20.40,28.12)	13.64(9.48,17.79)	24.27(21.09,27.45)	
Race						<0.01
Other Races	18.98(17.18,20.77)	8.68(6.70,10.65)	15.21(10.33,20.09)	7.59(4.42,10.75)	11.13(8.86,13.39)	
Hispanic	6.83(5.62,8.05)	3.21(2.36,4.06)	5.11(3.68,6.54)	4.82(2.82,6.81)	5.14(3.69,6.59)	
Non-Hispanic White	63.36(60.50,66.21)	82.00(79.15,84.86)	63.62（57.67,69.57）	78.92（73.97,83.87）	72.33（68.49,76.18）	
Non-Hispanic Black	10.83(9.39,12.27)	6.11(4.65,7.57)	16.06(12.29,19.83)	8.67(5.89,11.46)	11.40(9.14,13.65)	
Education Level						<0.01
High school or below	37.86(35.61,40.10)	34.05(30.26,37.84)	52.13(45.41,58.85)	44.35(38.06,50.64)	50.09(45.46,54.73)	
Some College	29.76(28.19,31.34)	34.45(31.27,37.18)	32.25(27.08,37.42)	31.04(24.03,38.06)	31.61(27.66,35.57)	
College graduate or above	32.38(30.03,34.73)	31.50(27.68,35.33)	15.62(9.94,21.30)	24.61(17.82,31.39)	18.29(14.06,22.52)	
BMI						<0.01
Normal	33.47(31.83,35.12)	22.68(19.75,25.60)	27.88(22.90,32.85)	21.88(16.37,27.40)	20.66(17.17,24.15)	
Overweight	33.79(32.56,35.03)	32.36(28.93,35.80)	28.46(23.46,33.46)	29.37(23.76,34.98)	31.40(27.98,34.83)	
Obesity	32.74(31.13,34.35)	44.96(41.35,48.57)	43.66(38.74,48.58)	48.75(42.23,55.26)	47.93(43.56,52.31)	
Blood pressure						<0.01
Hypertension	36.92(35.28,38.56)	66.37(62.74,70.00)	63.74(57.17,70.31)	58.84(51.88,65.81)	63.77(59.68,67.86)	
Normal	63.08(61.44,64.72)	33.63(30.00,37.26)	36.26(29.69,42.83)	41.16(34.19,48.12)	36.23(32.14,40.32)	
PIR						<0.01
Low income	22.04(20.42,23.65)	16.37(13.61,19.13)	29.76(23.51,36.01)	22.45(16.84,28.06)	24.27(19.78,28.76)	
Middle income	35.83(34.13,37.52)	36.00(32.49,39.50)	36.22(30.28,42.16)	37.89(30.75,45.02)	36.74(32.08,41.40)	
Elevated income	42.14(39.89,44.38)	47.63(43.03,52.24)	34.02(27.68,40.36)	39.66(31.66,47.67)	38.98(32.91,45.05)	
Smoking						<0.01
Current	18.69(17.41,19.97)	18.21(15.47,20.95)	27.50(22.36,32.63)	27.31(21.50,33.12)	20.56(17.17,23.95)	
Before	21.77(20.30,23.24)	32.89(29.41,36.36)	33.14(26.79,39.49)	29.07(23.55,34.59)	34.03(30.01,38.05)	

Never	59.54(57.76,61.32)	48.90(45.48,52.32)	39.36(33.15,45.58)	43.62(37.28,49.96)	45.41(41.18,49.65)	
PAL						<0.01
Moderate activities	54.56(53.24,55.88)	73.88(70.67,77.08)	72.08(66.44,77.72)	67.01(59.61,74.40)	73.28(68.99,77.58)	
Vigorous activities	45.44(44.12,46.76)	26.12(22.92,29.33)	27.92(22.28,33.56)	32.99(25.60,40.39)	26.72(22.42,31.01)	
Diabetes						<0.01
Yes	8.50 (7.63,9.36)	15.81(13.36,18.27)	22.68(19.11,26.24)	16.27(10.90,21.63)	18.40(15.33,21.48)	
No	91.51(90.64,92.37)	84.19(81.73,86.64)	77.32(73.76,80.89)	83.73(78.37,89.10)	81.60(78.52,84.67)	
Uric acid						<0.01
AH	84.35(83.33,85.38)	84.18(81.78,86.59)	80.11(75.97,84.25)	84.42(79.68,89.17)	82.04(78.71,85.36)	
Normal state	15.65(14.62,16.67)	15.82(13.41,18.22)	19.88(15.75,24.03)	15.58(10.83,20.32)	17.96(14.64,21.29)	
Cholesterol(mg/dl) †	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
LDL (mg/dl) †	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
HDL (mg/dl) †	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
Triglycerides(mg/dl) †	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
Creatinine(mg/dl) †	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
Albumin(mg/L) †	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout);

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Participants with OA are higher in non-Hispanic white (82.00% [95%CI: 79.15, 84.86]), hypertension (66.37% [62.74, 70.00]), elevated income (47.63% [43.03, 52.24]), moderate activities (73.88% [70.67, 77.08]), cholesterol (194.85±42.44) and HDL (57.40±36.73) than those without arthritis. Similar trends are observed in participants with RA, OA, other types of arthritis and those who responded with "don't know" when asked about the type of arthritis (Table 2).

And the proportion of participants who self-reported OA was the highest in arthritis. The proportion of AH is higher in participants with OA (84.18% [95%CI: 81.78, 85.59]) than in those with RA (80.11% [95%CI: 75.97, 84.25]) and unspecified (82.04% [95%CI: 78.71, 85.36]) arthritis types. But it is slightly lower than no arthritis (84.35% [95%CI: 83.33, 85.38]) and other arthritis (84.42% [95%CI; 79.68,89.17]) ($p<0.01$) (Table 2)

The association between AH and arthritis

Overall, AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07, 1.69) (Table 3). However, the association muted in different models after adjusting for demographic, socioeconomic factors, etc.

Table 3. Association between asymptomatic hyperuricemia and total arthritis.

	Unadjusted model	model 1	model 2	model 3
Control (Reference)	1	1	1	1
Total arthritis				
OR (95% CI)	1.34(1.07,1.69)	1.14(0.87,1.49)	1.11(0.83,1.48)	1.07(0.80,1.41)
P	0.012	<0.01	<0.01	<0.01

Model1: Adjusted for age, gender, and race.

Model2: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, diabetes, hypertension and smoking record.

Model3: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine, and albumin.

For participants aged 40-49 years, AH is significantly associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99). The association remained after adjusted for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36) (Table 4).

Table 4. The total arthritis was analyzed stratified by gender, age, and race

	Model 1 (OR,95%, P)	Model 2 (OR,95%, P)	Model 3 (OR,95%,P)
Gander			
Male	1	1	1
Female	0.753(0.633,0.896)0.002	0.730 (0.608,0.877) 0.001	0.712(0.582,0.872)0.001
Age			
20-29	1	1	1
30-39	1.788(1.078,2.966)0.025	1.718(1.003,2.940)0.048	1.181(0.635,2.199)0.595
40-49	1.957(1.285,2.981)0.002	2.002(1.941,3.358)0.009	1.324(0.721,2.432)0.362
50-59	1.409(0.989,2.008)0.057	1.472(0.963,2.251)0.074	0.975(0.582,1.632)0.932
60-69	1.034(0.718,1.489)0.856	1.076(0.700,1.653)0.737	0.721(0.436,1.192)0.200
70+	1.106(0.789,1.549)0.556	1.122(0.725,1.737)0.602	0.739(0.426,1.282)0.278
Race			
Other Race	1	1	1
Hispanic	1.604(1.136,2.264)0.008	1.582(1.056,2.371)0.027	1.456(0.962,2.203)0.075
Non-Hispanic White	0.895(0.696,1.150)0.381	1.040(0.786,1.376)0.780	0.971(0.732,1.288)0.839
Non-Hispanic Black	2.017(1.471,2.765)0.000	2.305(1.622,3.276)0.000	2.203(1.536,3.160)0.000

Model1: Adjusted for age, gender, and race.

Model 2: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking record.

Model 3: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine and albumin.

Among non-Hispanic black participants, AH was significantly associated with arthritis. (OR=2.02, 95%CI: 1.47, 2.77). The results kept significant adjusting for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.31, 95%CI: 1.62, 3.28) and for cholesterol, LDL, HDL, triglyceride, creatinine, and albumin (OR=2.20,95%CI: 1.55, 3.16) (Table 4).

Compared with male participants, female participants with AH showed a higher likelihood of OA (OR=1.35, 95%CI: 1.14, 1.60). However, for RA (OR: 1.08, 95%CI: 0.83, 1.41), other forms of arthritis (OR: 1.00, 95%CI: 0.78, 1.29), and the 'Unspecified' category (OR: 0.99, 95%CI: 0.82, 1.20), the observed associations were not statistically significant.

Notably, this trend was more prominent within the OA subgroup (sTable 2). Among participants aged > 50 years, there is a significant association between AH and different types of arthritis (including OA, RA, other, unspecified). More importantly, the strength of this association increased with age, specifically for 50-59 years, 60-69 years, 70+ years.

Discussion

Based on 12 years of nationally representative data from NHANES, our findings indicated an association between AH and the arthritis, with a notable focus on OA. The correlation was present before adjusting the model. However, after adjusting for additional variables such as cholesterol and creatinine, the correlation weakened, suggesting that the relationship between AH and arthritis (including OA) might not be independent and could be influenced by metabolic and physiological factors like cholesterol and creatinine[29]. Our research findings suggest a significant correlation between asymptomatic hyperuricemia (AH) and arthritis among non-Hispanic Black individuals, possibly due to metabolic syndrome-related metabolic abnormalities being less sensitive in identifying elevated uric acid levels in non-Hispanic Black populations [30].

Although hyperuricemia is a major contributor to the development of gouty arthritis, accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic arthritis and spondylarthritis[31-33]. In vitro studies on synoviocytes from healthy and RA subjects revealed that monosodium urate crystals could increase the release of the inflammatory cytokine IL-6, the chemokine CXCL8 and the matrix metalloproteinase-1[34]. The injection of urate crystals in vivo leads to produce main mediators in the pathogenesis of PsA, such as IL-17 [35]. The hyperuricemia not only play an important role the development and progression of psoriatic arthritis, but also affect severity of clinical manifestations and degree of inflammation[36]. Monosodium urate crystals interact with articular tissues to influence the development of axial spondyloarthritis as monosodium urate crystal deposition associated with the progress of radiographic grade at the sacroiliac joint[18, 37].

Our data indicate that AH may serve as a marker for potential risk in relation to OA. [22]. An increasing body of evidence suggests that AH, characterized by elevated serum uric acid levels without any symptoms of gout or kidney stone disease, may be associated with an increased risk of OA, particularly in weight-bearing joints such as the knee[16, 38,

39]. The relationship between AH and arthritis is complex and multifaceted, and the exact nature of this relationship is not yet clear. Hyperuricemia may promote the development of arthritis via deposition of urate crystals in the joints, promoting chronic low-grade inflammation, and exacerbating oxidative stress[20, 22, 40]. However, it is also possible that the association between hyperuricemia and arthritis is partially due to common risk factors such as obesity and metabolic syndrome[41, 42]. Further research is needed to better understand the relationship between these two conditions and to identify potential therapeutic targets for the prevention or treatment of arthritis in patients with hyperuricemia.

The intimate relationship between hyperuricemia and OA may re-purpose FDA-approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids[43]. However, these drugs could only use to relieve the clinical symptoms but not decrease the onset of arthritis. In accordance with our findings, another study also supports the significant association between arthritis and hypertension[44]. In recent years, there has been growing interest in exploring the role of urate-lowering therapy in the treatment of OA[45]. Urate crystal deposition can directly damage cartilage, stimulate the production of pro-inflammatory cytokines, and lead to inflammation and cartilage degradation[46]. Urate-lowering therapy drugs such as allopurinol and febuxostat have been shown to have anti-inflammatory properties, inhibit the production of reactive oxygen species, reduce the expression of pro-inflammatory cytokine[47-49]. Our results raise the possibility that pharmacological treatment of AH via a treat-to-target (T2T) strategy may decrease incident of arthritis, especially for OA. The T2T strategy involves targeting specific uric acid levels and adjusting drug therapy accordingly to achieve this goal[50, 51].

Our findings highlight those female participants with AH are more likely to develop arthritis, especially for OA, than male participants, and ageing may exaggerate this trend. Among adults in the US, mean uric acid levels were 6.0 mg/dl in men and 4.8 mg/dl in women, and hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[11]. Studies have also shown that hyperuricemia is more common in men over 30 and women over 50[52]. The gender and age associated increase in serum uric acid levels may be explained by menopause in women and alcohol consumption in men[53]. Menopause can

lead to an increase in serum uric acid levels, while postmenopausal hormone replacement therapy may be associated with a decrease in serum uric acid levels[54]. The difference in serum uric acid levels between men and women is due to the increased renal uric acid clearance caused by estrogen in women before menopause[55]. Serum Urate levels were significantly associated with knee OA as determined by osteophytosis in women but not in men[56]. Female typically have a higher prevalence of hand and knee arthritis than males, females also tend to have more severe knee OA, particularly after menopausal age[57].

The strength of our study was the use of data from a large, nationally representative sample. However, results should be interpreted with caution with inherent limitation. First, it is not possible to interpret the findings from a causal point of view due to the cross-sectional approach. Prospective study and mendelian randomization study are needed to further investigate the relationship between the AH and arthritis, especially OA. Second, recall bias may affect the accuracy of prevalence estimates although this study used CDC-recommended self-reported and physician-diagnosed arthritis as case definitions[24, 58]. Third, our result might be charged with choosing a single number to represent prevalent of arthritis in the US population as it only included adults in the national non-institutionalized population of the country[59]. Fourth, medication use for the participants was not included in this study. Finally, we had limited information on the involvement of OA in each participant, such as imaging and treatment procedures.

In summary, our study results suggest that AH patients may benefit from close monitoring for the development of arthritis, understanding the relationship between hyperuricemia and arthritis, and identifying factors that contribute to their increased risk of these diseases, which may be of great significance for the prevention and management of these conditions.

Contributors

Prof. Jieruo Gu is the guarantor of the study and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Zhenguo Liang, Dr. Dongze Wu, and Prof. Jieruo Gu, conceived and designed the study, performed the analysis, and wrote the paper. Prof. Hua Zhang participated in the revision and refinement of the content. All authors read and commented on the manuscript and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclaimer

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Declaration of interests

The authors declare no conflict of interests.

Ethical approval

The data released from the National Health and Nutrition Examination Survey did not require informed patient consent. This study used an anonymized publicly available data set with no identifiable information on the survey participants, and thus did not require ethics approval.

Data sharing

The data used for the analyses are publicly available from the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC) in the United States (https://www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

Supplemental appendix

sTable 1. Characteristics of participants included in this study.

sTable 2. Subgroup analysis of the association of arthritis subtype (RA, OA, other and unspecified) and AH.

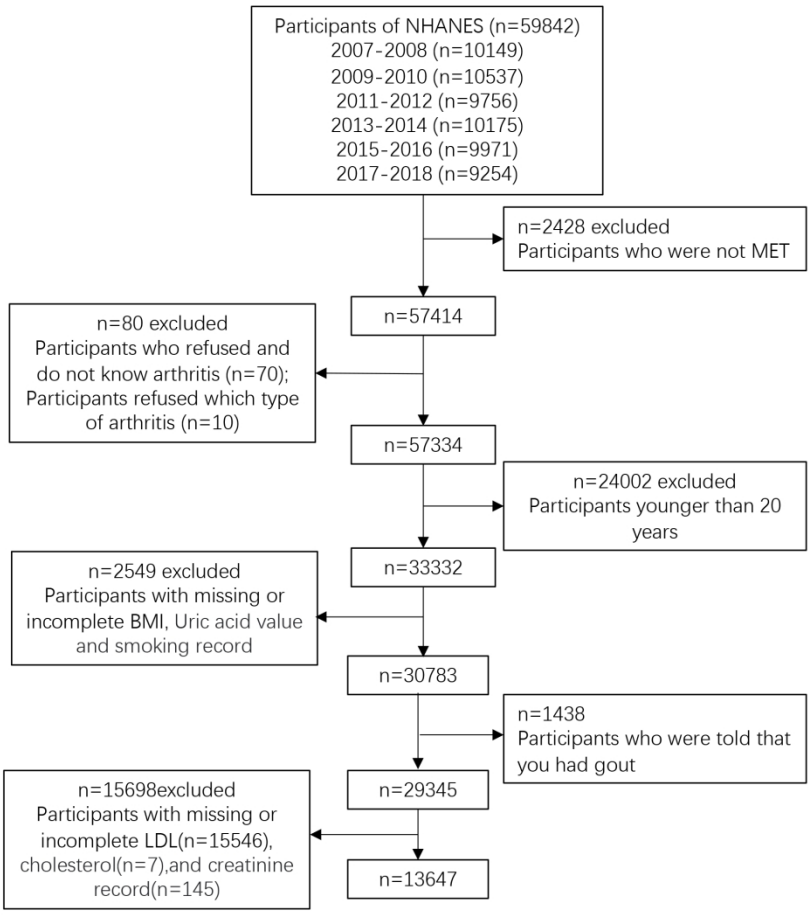

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

188x175mm (300 x 300 DPI)

Supplementary materials

The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

Supplementary Tables

sTable1. Characteristics of participants included in this study

sTable2. Subgroup analysis of the association of arthritis subtype (RA, OA, Other and Unspecified) and AH.

Supplementary Table 1. Characteristics of participants included in this study

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	p
N*	2330	2528	2229	2367	2067	2126	
Uricacid							0.438
NA	83.65(81.60,85.69)	84.50(82.38,86.62)	84.71(82.87,86.64)	83.55(81.95,85.15)	84.13(82.09,86.17)	83.61(80.70,86.53)	
AH	16.35(14.01,18.40)	15.50(13.38,17.62)	15.29(13.46,17.13)	16.45(14.85,18.05)	15.87(13.83,17.91)	16.39(13.47,19.30)	
Gender							0.279
Male	47.25(45.60,48.89)	45.56(43.56,47.55)	47.90(45.04,50.75)	47.69(45.61,49.77)	47.36(45.31,49.42)	48.09(44.95,51.22)	
Female	52.75(51.11,54.40)	54.44(52.45,56.44)	52.10(49.25,54.96)	52.31(50.23,54.39)	52.64(50.58,54.69)	51.91(48.78,55.05)	
Age							<0.01
20-29	19.13(16.42,21.85)	19.35(16.80,21.90)	18.23(15.01,21.45)	18.40(15.73,21.08)	16.67(14.61,18.72)	19.86(16.81,22.90)	
30-39	18.20(15.96,20.43)	16.98(14.62,19.35)	18.53(15.67,21.39)	17.24(15.16,19.31)	15.59(14.04,17.15)	18.76(15.92,21.60)	
40-49	20.97(17.50,24.44)	21.50(19.52,23.49)	18.86(15.20,22.52)	19.43(16.80,22.07)	18.56(15.67,21.45)	15.71(13.13,18.28)	
50-59	19.29(16.77,21.80)	19.37(16.98,21.77)	19.08(17.07,21.08)	18.17(15.58,20.76)	18.81(17.09,20.54)	19.93(16.84,23.02)	
60-69	11.44(9.42,13.46)	11.18(9.90,12.46)	14.03(12.10,15.96)	14.71(12.03,17.38)	19.21(16.43,22.00)	14.81(11.45,18.16)	
70+	10.98(9.65,12.30)	11.60(10.10,13.10)	11.26(9.65,12.88)	12.05(10.37,13.73)	11.16(9.36,12.96)	10.95(8.93,12.97)	
Race/Ethnicity							<0.01
Other Race	13.87(10.43,17.31)	16.55(11.72,21.38)	15.80(11.44,20.16)	16.88(12.75,21.02)	17.24(13.58,20.90)	19.91(16.40,23.42)	
Hispanic	5.09(2.60,7.58)	5.84(2.94,8.74)	6.74(3.84,9.64)	5.67(2.34,8.61)	6.74(3.88,9.59)	6.86(5.00,8.72)	
Non-Hispanic White	70.37(63.63,77.11)	66.91(60.23,73.59)	68.04(61.22,74.87)	67.07(60.01,74.13)	65.74(57.81,73.66)	61.96(57.22,66.69)	

Non-Hispanic Black	10.67(6.63,14.70)	10.70(8.67,12.72)	9.42(5.94,12.90)	10.37(7.68,13.07)	10.29(5.86,14.71)	11.27(7.61,14.93)	
Education Level							<0.01
High school or below	43.02(37.88,48.16)	41.31(37.13,45.52)	37.42(31.97,42.87)	36.42(30.79,42.04)	36.46(30.23,42.68)	39.61(36.03,43.19)	
Some college	28.45(26.32,30.58)	29.63(26.71,32.56)	31.10(27.90,34.30)	32.90(29.91,35.90)	31.18(27.20,35.16)	29.91(25.07,34.76)	
College graduate or above	28.53(24.06,33.00)	29.05(25.76,32.33)	31.48(25.02,37.94)	30.68(26.29,35.07)	32.36(25.35,39.37)	30.47(24.72,36.23)	
BMI							<0.01
Normal	33.39(31.60,35.19)	32.13(28.74,35.52)	31.68(27.63,35.73)	31.24(28.78,33.70)	27.17(23.38,30.96)	29.29(25.52,33.05)	
Overweight	35.11(32.97,37.26)	32.96(30.44,35.48)	33.36(31.12,35.60)	33.31(30.91,35.70)	32.66(31.03,34.28)	31.53(29.18,33.8)	
Obesity	31.49(28.61,34.37)	34.91(32.02,37.79)	34.96(31.50,38.42)	35.45(33.20,37.70)	40.17(36.34,44.00)	39.18(35.37,43.00)	
Blood pressure							<0.01
Hypertension	40.92(37.47,44.37)	40.38(36.47,44.30)	45.82(41.97,49.68)	43.84(39.24,48.43)	44.44(40.49,48.40)	46.99(43.71,50.28)	
Normal	59.08(55.63,62.53)	59.62(55.70,63.53)	54.18(50.32,58.03)	56.16(51.57,60.76)	55.56(51.60,59.51)	53.01(49.72,56.29)	
PIR							<0.01
Low income	19.38(16.16,22.61)	21.90(19.24,24.56)	24.29(20.21,28.38)	25.33(19.07,31.59)	19.64(16.45,22.82)	20.01(17.46,22.56)	
Middle income	33.99(30.47,37.52)	37.50(33.75,41.26)	35.70(31.24,40.17)	33.69(30.70,36.68)	37.50(34.14,40.87)	37.61(33.36,41.86)	
High income	46.62(41.80,51.44)	40.60(36.83,44.36)	40.00(33.29,46.72)	40.98(34.20,47.76)	42.86(37.83,47.88)	42.38(37.89,46.88)	
Somking							0.01
Current	21.61(18.39,24.83)	18.98(17.51,20.45)	20.06(16.75,23.36)	19.50(15.86,23.14)	18.73(15.50,21.97)	17.47(14.68,20.27)	
Before	24.99(22.25,27.73)	24.21(20.55,27.87)	23.04(20.16,25.92)	23.68(20.64,26.72)	26.46(22.62,30.31)	24.90(22.47,27.32)	
Never	53.40(49.73,57.07)	56.80(53.00,60.61)	56.90(53.76,60.05)	56.82(52.86,60.78)	54.81(50.57,59.04)	57.63(54.64,60.62)	

PAL							<0.01
Moderate activities	58.98(55.40,62.57)	62.32(59.17,65.48)	61.71(57.96,65.46)	62.05(59.40,64.70)	57.56(54.23,60.90)	52.20(49.94,54.47)	
Vigorous activities	41.02(37.43,44.60)	37.68(34.52,40.83)	38.29(34.54,42.04)	37.95(35.30,40.60)	42.44(39.10,45.77)	47.80(45.53,50.06)	
Diabetes							<0.01
Yes	10.17(8.32,12.03)	9.47(8.21,10.74)	10.20(8.31,12.09)	10.34(8.83,11.84)	12.25(9.95,14.55)	12.14(9.78,14.49)	
No	89.83(87.97,91.68)	90.53(89.26,91.79)	89.80(87.91,91.69)	89.66(88.16,91.17)	87.75(85.45,90.05)	87.86(85.51,90.22)	
With or without arthritis							<0.01
No arthritis	74.05(70.64,77.47)	74.90(72.43,77.38)	77.19(73.85,80.53)	75.09(72.40,77.78)	73.16(70.09,76.24)	74.47(70.56,78.38)	
Arthritis	25.95(22.53,29.36)	25.10(22.62,27.57)	22.81(19.47,26.15)	24.91(22.22,27.60)	26.84(23.76,29.91)	25.53(21.62,29.44)	
OA	8.70(6.56,10.85)	9.56(8.30,10.82)	11.30(8.92,13.68)	13.88(11.87,15.89)	12.92(10.99,14.86)	12.44(9.32,15.55)	
RA	3.57(2.87,4.27)	4.11(3.18,5.04)	3.90(2.78,5.02)	3.09(2.15,4.02)	3.59(2.53,4.64)	4.04(2.82,5.25)	
Other	3.54(2.56,4.52)	3.64(2.80,4.47)	2.88(1.39,4.37)	2.98(2.05,3.91)	3.33(1.66,5.01)	3.04(1.78,4.30)	
Unspecified	10.13(8.22,12.05)	7.79(6.41,9.17)	4.73(3.14,6.33)	4.96(4.03,5.89)	6.99(5.25,8.73)	6.02(4.66,7.37)	
Cholesterol(mg/dl)†	194.90±40.98	195.00±39.66	191.78±39.95	188.44±39.94	190.31±41.06	186.04±40.55	<0.01
LDL(mg/dl)†	115.60±35.83	116.32±34.82	114.41±34.74	111.74±35.10	112.89±35.82	110.72±35.69	<0.01
HDL(mg/dl)†	54.15±15.40	54.40±15.95	53.78±14.93	54.58±16.11	55.97±17.56	54.02±15.74	<0.01
Triglyceride(mg/dl)†	125.72±66.36	121.43±64.17	117.95±64.42	110.61±65.08	107.26±63.05	106.48±63.30	<0.01
Creatinine(mg/dl)†	123.56±74.93	124.01±74.60	125.83±78.25	119.58±74.02	126.23±77.54	136.33±83.94	<0.01
Albumin(mg/dl)†	58.18±663.81	33.09±182.80	37.78±211.82	40.30±250.06	51.49±338.92	56.01±379.49	0.105

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL with no gout); NA: no-hyperuricemia.

Supplementary Table 2. Subgroup analysis of the association of arthritis subtype (RA, OA, Other and Unspecified) and AH

	OA (OR,95%, P)	RA (OR,95%, P)	Other (OR,95%, P)	Unspecified (OR,95%, P)
Gander				
Male	1	1	1	1
Female	1.35(1.14,1.60)0.00	1.08(0.83,1.41)0.59	1.00(0.78,1.29)1.00	0.99(0.82,1.20)0.96
Age				
20-29	1	1	1	1
30-39	0.36(0.27,0.49)0.00	0.36(0.24,0.54)0.00	0.35(0.23,0.55)0.00	0.38(0.27,0.53)0.00
40-49	0.80(0.62,1.04)0.97	0.99(0.71,1.38)0.96	0.88(0.64,1.21)0.44	0.95(0.70,1.30)0.74
50-59	2.16(1.72,2.72)0.00	2.12(1.50,3.00)0.000	1.35(1.00,1.83)0.51	1.90(1.44,2.49)0.00
60-69	4.18(3.26,5.35)0.00	3.34(2.50,4.46)0.000	1.69(1.13,2.53)0.01	2.70(1.92,3.78)0.00
70+	5.50(4.18,7.22)0.00	4.57(3.40,6.15)0.000	1.51(0.99,2.33)0.06	4.24(3.16,5.69)0.00

RA: rheumatoid arthritis; OA: osteoarthritis; AH: asymptomatic hyperuricemia

All data were adjusted for gender, age, race, BMI, education level and poverty to income ratio, hypertension, ever cigarette smoking and diabetes.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 13-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

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The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

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Conflict of Interest: The authors confirm that there are no conflicts of interest.

Running Head: Association between asymptomatic hyperuricemia and risk of arthritis.

Abstract

Background

Arthritis is thought to be closely related to serum uric acid. The study aims to assess the association between asymptomatic hyperuricemia (AH) and arthritis.

Methods

A multistage, stratified cluster was used to conduct a cross-sectional study of adult U.S. civilians aged≥ 20 years from the 2007-2018 National Health and Nutrition Examination Survey (NHANES). Participants with hyperuricemia and without hyperuricemia prior to gout were included. A questionnaire was used to determine whether participants had arthritis and the type of arthritis. Logistic regression was used to investigate the association between hyperuricemia and arthritis.

Result

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA) increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30). Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69), but the association was muted after adjusting demographic and socioeconomic factors. For participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99) and the relationship remained after adjusting for education level, income to poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

Conclusion

Our data identified AH as the risk factor for incident arthritis, especially for OA, which might be exaggerated in aged population and female population.

Keywords: Arthritis, Asymptomatic hyperuricemia, Association, Risk

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study comprehensively assessed the association between asymptomatic hyperuricemia and arthritis in the United States population aged≥ 20 years during 2007-2018.
- The respondents were intricately weighted, and adjustments were made for different covariates to reduce the likelihood of interference from confounding factors.
- Due to the observational study design, future randomized control study or longitudinal study should be conducted to validate the causal relationship between asymptomatic hyperuricemia and onset of arthritis other than gouty arthritis.
- Our findings report trends through 2007-2018, it will be important to continue to examine how the COVID-19 pandemic has potentially influence such trends when data from 2019 and 2022 become available.

Introduction

More than one in five adults in the United States had doctor-diagnosed arthritis, and arthritis-attributable activity limitations significantly increased over time independent of the population ageing[1]. By 2040, the adults with doctor-diagnosed arthritis are projected to increase 49% to 78.4 million (1 in 4 US adults), and the arthritis-attributable activity limitation will increase 52% to 34.6 million (1 in 9 adults)[2]. High medical care expenditures and earnings losses attributable to arthritis signaling the need for identification of disease and risk factors that are in most need for interventions[3]. OA as the most common form of arthritis, involves structural changes in the articular cartilage, subchondral bones, ligaments, bursae, synovium, and muscles surrounding the joint[4]. From 1990 to 2019, the global age standardized incidence rate of OA increased from 474 to 492 per 100, 000 population and expected to increase due to global population ageing[5, 6]. About 20% of the general population affected by hyperuricemia, which might be more prominent in male and aged population[7]. Prior research has consistently shown a significant correlation between arthritis, particularly OA and rheumatoid arthritis (RA), and hypertension[8]. The intricate relationship between metabolic processes and arthritis, alongside the interplay between metabolic and immunological factors, is garnering heightened attention. Metabolic syndrome's implication in various forms of arthritis, such as OA, is increasingly recognized. [9, 10].

In 2007-2016, the prevalence of hyperuricemia, gout, and the urate-lowering therapy among patients with gout remained stable[11]. The true significance of asymptomatic hyperuricemia (AH) as a risk factor for incident gout becomes apparent when considering that only half of patients with longstanding hyperuricemia develop clinically evident gout over a 15-year period.[12, 13]. Advanced imaging, including ultrasonography or dual-energy CT, demonstrated approximately 15–40% of patients with chronic hyperuricemia have silent monosodium urate crystal deposition[14]. As the crystallization of monosodium urate marks the progression of hyperuricemia towards gout, it remains uncertain whether hyperuricemia contributes to other forms of arthritis.[15].

Both hyperuricemia and OA are influenced by common risk factors such as obesity and aging. This shared relationship between risk factors suggests a potential connection between the hyperuricemia and OA, with intraarticular urate contributing to crystallization and cartilage disruption in the context of these shared risk factors.[16]. The predilection for both OA and gout occur in the same joints strongly suggest that OA may predispose to the localized deposition of monosodium urate crystals, which influence structural joint damage[17-19]. Monosodium urate crystals have been shown to inhibit the viability and function of human chondrocytes in vitro with a dose-dependent manner[20]. Death of chondrocytes can lead to an increase in urate, which may even promote crystal deposition on the cartilage, further aggravating OA progression[16]. Monosodium urate crystals inhibit osteocyte viability and, through interactions with macrophages, indirectly promote a shift in osteocyte function that favors bone resorption and inflammation[21]. Uric acid is a danger signal of increasing risk OA through inflammasome activation[22]. Therefore, we hypothesized that hyperuricemia prior to gout was associated with OA. The aim of this study was to i) ascertain the association between AH and arthritis, ii) determine the association between AH and OA, iii) investigate the effect of age and gender on such association.

Patients and methods

Patient and Public Involvement

NHANES is an ongoing longitudinal survey conducted by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the United States through a series of interviews and examination items. The NHANES is conducted

biennially in a nationally representative, non-institutionalized civilian population, and use a hierarchical multi-stage probabilistic clustering design to select a representative sample of over-sampled participants. The sampling methods and examination information used in this study have been described in detail elsewhere[23]. NHANES was reviewed and approved by the NCHS Research Ethics Committee. All manipulations of the NHANES were carried out in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants in NHANES.

The study used data from NHANES database for the 2007-2018 study cycle (n=59,842) and excluded those who did not participate in the examination (n=2,428).We excluded participants who refused and don't know ever had or hadn't arthritis, refused to answer which type of arthritis (n=80), who are younger than 20 years old (n=24,002), who have missing and incomplete BMI, uric value, and smoking record (n=2,549). We also excluded participants who were told that you had gout(n=1,438) and participants with missing or incomplete low-density lipoprotein (LDL), cholesterol, and creatinine record. In the end, this study consisted of 13, 647 eligible participants (Figure 1), which is representative of the population size of 87,901,487.

Conditions of arthritis

The status of arthritis was classified using questionnaires. Participants aged 20 years and older were asked "Has a doctor or other health professional ever said that you had arthritis?". If the participants gave a positive answer, they were further asked "Which type of arthritis was it?". Participants' responses included RA, OA, other, do not know type, and refuse to answer. Individuals were excluded from the current analysis if their self-reported type of arthritis declined to answer. A consistent relationship between self-reports of arthritis and a clinical diagnosis of arthritis has been demonstrated in previous reports[24].

Hyperuricemia

Hyperuricemia is an elevated level of uric acid in the blood. The normal upper limit for serum uric acid (SUA) at physiological levels is 6.8 mg/dL. This is the saturation point at which urate may precipitate under physiological conditions[25, 26]. We put SUA>6.8 mg/dL was defined as hyperuricemia, and SUA≤6.8 mg/dL is defined as the normal state.

Covariates

Covariates are identified in statistical models by means of interview responses and

examinations. Covariates that could confound the association between OA and AH were selected based on the results of interviews and examinations in the NHANES database. These factors were chosen to screen for variables that might be associated with OA risk and/or could be associated with AH. This selection aimed to minimize potential confounding variables in the association between OA and AH. The chosen covariates included self-reported demographic characteristics, such as gender, age, race, education level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level (PAL), and diabetes.

Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race is divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other races. Education is grouped as high school or below, some college and college graduate or above. BMI is calculated from measured weight and height determined by standard NHANES protocols[27]. BMI is categorized as three groups: Normal (<18.5kg/m^2), Overweight (18.5–24.9kg/m^2) and Obesity (≥25 kg/m^2). Participants with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg are defined as hypertension[28]. PIR as a socioeconomic indicator is stratified into three levels: Low income (PIR < 1.3), Middle income (1.3 ≤ PIR < 3.5) and High income (PIR≥ 3.5).

Smoking status is categorized according to interview results as current (smoked more than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which includes moderate work activity, walking or cycling, moderate recreational activity, and vigorous activity, which includes vigorous work activity and vigorous recreational activity. Participants with self-reported diabetes had either a diabetes physician's diagnosis of diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance (OGTT), or/and HbA1c≥6.5%. Laboratory data included cholesterol, LDL, High-density lipoprotein (HDL), triglycerides, creatinine, and albumin.

Statistical analysis

Design factors involving complex weighting, clustering, and stratification in the NHANES database. Statistical analysis was conducted using STATA (version 16). Complex stratification designs were considered using appropriate sample weights in

accordance with NHANES analytical reporting guidelines. In baseline study characteristics, means and standard errors (SEs) were used for continuous variables. Categorical variables were expressed as numbers and percentages. Chi-square test and t-test were used for categorical and continuous variables, respectively. A weighted logistic regression was used to assess the association between OA and AH and to control for confounding factors. Finally, subgroup analysis was performed using hierarchical multivariate regression. The 95% confidence intervals and p-values were calculated. A two-tailed test with p-values less than 0.05 are considered significant.

Results

The characteristics of study participants

A total of 13,647 participants were eligible and included in the analysis from 2007-2008 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81% (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09% (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69). Between 2007-2008 and 2017-2018, the proportion of high school or below decreased, which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06, 33.00) to 30.47% (95%CI: 24.72, 36.23) (sTable 1).

During the past 12 years, the percentage of participants with arthritis changed from 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while the proportion of those who don't know arthritis decreased from 10.13% (95%CI: 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed a clear upward trend during the 12 years, from 8.70% (95%CI: 6.56, 10.85) in 2007-2008 to 12.44% (95%CI: 9.32, 15.55) in 2017-2018 ($p<0.01$) (sTable 1).

The 50-59 age group displayed the highest percentage of individuals with AH (19.39% [95%CI: 17.17, 21.61]) among all the age groups that were examined. A larger proportion of males (77.17% [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI:

20.63, 25.04]) (Table 1). There are significant differences in race between participants with and without AH (p<0.01). Participants in the AH group had higher levels of obesity, hypertension, diabetes, LDL, triglycerides, and creatinine than those in the normal state group (Table 1).

The prevalence of patients with OA and AH (11.40% [95%CI: 9.56, 13.24]) is considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56, 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and unspecified: 7.54% (95%CI: 6.03, 9.05)) (p<0.01) (Table 1).

The characteristics of hyperuricemia and arthritis

The higher frequency of participants with arthritis, including OA, RA, other forms, and those who were unaware of having arthritis, among individuals aged over 50 years, suggests that age may be a contributing factor to the prevalence of arthritis in this population (Table 2). The characteristics of the 13,647 participants included in our study with self-reported OA, RA, other, and Unspecified are presented using weighted statistics (Table 1). The prevalence of the four types of arthritis was higher among female participants than among male participants, which was most notable in OA (female: 65.94% vs male 34.06%) (Table 2).

Table 1. Baseline characteristics of high uric acid group versus the normal state group.

Characteristics	Normal state	AH	p value
N*	11387	2260	
Gender			<0.01
Male	41.66(40.55,42.76)	77.17(74.96,79.37)	
Female	58.34(57.24,59.45)	22.83(20.63,25.04)	
Age			<0.01
20-29	18.86(17.56,20.15)	17.30(15.07,19.53)	
30-39	18.03(16.98,19.07)	15.15(12.83,17.48)	
40-49	19.44(18.21,20.67)	17.39(14.72,20.05)	
50-59	19.05(17.98,20.12)	19.39(17.17,21.61)	
60-69	14.01(12.95,15.07)	15.66(13.36,17.95)	
70+	10.62(9.91,11.32)	15.11(13.21,17.00)	
Race			<0.01
Other Races	17.22(15.50,18.93)	14.33(12.20,16.47)	
Hispanic	6.32(5.21,7.44)	5.39(4.02 ,6.76)	
Non-Hispanic White	66.30(63.54,69.05)	68. 32(64.74,71.91)	
Non-Hispanic Black	10.16(8.80,11.53)	11.96(9.82,14.09)	
Education Level			0.137
High school or below	38.72(36.58,40.86)	40.33(37.04,43.63)	
Some College	30.44(28.96,31.92)	31.18(28.20,34.17)	
College graduate or above	30.84(28.51,33.16)	28.49(25.66,31.31)	
BMI			<0.01
Normal	34.09(32.60,35.58)	13.41(11.57,15.25)	
Overweight	33.07(32.07,34.08)	33.41(30.59,36.23)	
Obesity	32.83(31.48,34.19)	53.18(49.93,56.43)	
Blood pressure			<0.01
Hypertension	40.84(39.20,42.49)	59.45(56.85,62.06)	
Normal	59.16(57.51,60.80)	40.55(37.94,43.15)	
PIR			0.03
Low income	22.36(20.66,24.06)	18.98(17.00,20.97)	
Middle income	35.84(34.22,37.47)	36.73(33.94,39.53)	

Elevated income	41.79(39.48,44.11)	44.28(40.87,47.69)	
Smoking			<0.01
Current	19.72(18.32,21.11)	17.51(15.41,19.62)	
Before	23.23(21.86,24.60)	31.37(28.28,34.47)	
Never	57.06(55.32,58.79)	51.11(48.07,54.16)	
PAL			0.744
Moderate activities	59.26(57.72,60.81)	58.20(55.43,60.97)	
Vigorous activities	40.74(39.19,42.28)	41.80(39.03,44.57)	
Diabetes			<0.01
Yes	9.85(8.99,10.70)	15.68(14.06,17.30)	
No	90.15(89.30,91.01)	84.32(82.70,85.94)	
Arthritis			<0.01
No arthritis	75.13(73.67,76.59)	73.29(70.69,75.89)	
OA	11.54(10.55,12.53)	11.40(9.56,13.24)	
RA	3.54(3.11,3.97)	4.62(3.56,5.69)	
Other	3.24(2.69,3.79)	3.14(2.12,4.17)	
Unspecified	6.55(5.88,7.22)	7.54(6.03,9.05)	
Cholesterol(mg/dl) †	191.01±40.22	192.23±41.65	0.1924
LDL (mg/dl)†	113.39±35.07	115.48±36.82	0.0088
HDL (mg/dl)†	55.58±15.89	48.87±15.10	<0.01
Triglycerides(mg/dl) †	110.45±62.12	139.39±73.24	<0.01
Creatinine(mg/dl)†	122.00±75.58	144.47±82.80	<0.01
Albumin(mg/dl)†	35.52±320.96	97.29±565.77	<0.01

BMI: body mass index; PIR: poverty income ratio; PA: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout).

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Table 2. Baseline characteristics of arthritis group versus the non-arthritis group.

Characteristics	No Arthritis	OA	RA	Other	Unspecified	p value
N*	10089	1402	662	408	1086	
Gender						<0.01
Male	50.40(49.20,51.61)	34.06(31.15,36.97)	40.89(35.23,46.54)	40.90(34.65,47.15)	42.48(38.96,46.01)	
Female	49.60(48.39,50.80)	65.94(63.03,68.85)	59.11(53.46,64.77)	59.10(52.85,65.35)	57.52(53.99,61.04)	
Age						<0.01
20-29	24.10(22.69,25.52)	1.15(0.57,1.73)	2.62(0.30,4.94)	3.98(1.36,6.60)	3.17(1.79,4.55)	
30-39	21.40(20.16,22.64)	5.15(3.81,6.49)	6.11(3.79,8.43)	9.40(5.76,13.05)	6.35(4.47,8.24)	
40-49	20.74(19.35,22.14)	11.11(9.08,13.14)	15.63(11.52,19.73)	22.38(17.09,27.67)	15.00(11.89,18.10)	
50-59	16.53(15.39,17.66)	25.56(22.65,28.48)	26.90(20.60,33.20)	29.34(23.07,35.60)	27.60(23.49,31.71)	
60-69	10.22(9.19,11.25)	29.91(26.73,33.09)	24.48(19.59,29.36)	21.26(14.97,27.56)	23.61(20.04,27.19)	
70+	7.01(6.40,7.61)	27.11(24.11,30.12)	24.26(20.40,28.12)	13.64(9.48,17.79)	24.27(21.09,27.45)	
Race						<0.01
Other Races	18.98(17.18,20.77)	8.68(6.70,10.65)	15.21(10.33,20.09)	7.59(4.42,10.75)	11.13(8.86,13.39)	
Hispanic	6.83(5.62,8.05)	3.21(2.36,4.06)	5.11(3.68,6.54)	4.82(2.82,6.81)	5.14(3.69,6.59)	
Non-Hispanic White	63.36(60.50,66.21)	82.00(79.15,84.86)	63.62（57.67,69.57）	78.92（73.97,83.87）	72.33（68.49,76.18）	
Non-Hispanic Black	10.83(9.39,12.27)	6.11(4.65,7.57)	16.06(12.29,19.83)	8.67(5.89,11.46)	11.40(9.14,13.65)	
Education Level						<0.01
High school or below	37.86(35.61,40.10)	34.05(30.26,37.84)	52.13(45.41,58.85)	44.35(38.06,50.64)	50.09(45.46,54.73)	
Some College	29.76(28.19,31.34)	34.45(31.27,37.18)	32.25(27.08,37.42)	31.04(24.03,38.06)	31.61(27.66,35.57)	
College graduate or above	32.38(30.03,34.73)	31.50(27.68,35.33)	15.62(9.94,21.30)	24.61(17.82,31.39)	18.29(14.06,22.52)	
BMI						<0.01
Normal	33.47(31.83,35.12)	22.68(19.75,25.60)	27.88(22.90,32.85)	21.88(16.37,27.40)	20.66(17.17,24.15)	
Overweight	33.79(32.56,35.03)	32.36(28.93,35.80)	28.46(23.46,33.46)	29.37(23.76,34.98)	31.40(27.98,34.83)	
Obesity	32.74(31.13,34.35)	44.96(41.35,48.57)	43.66(38.74,48.58)	48.75(42.23,55.26)	47.93(43.56,52.31)	
Blood pressure						<0.01
Hypertension	36.92(35.28,38.56)	66.37(62.74,70.00)	63.74(57.17,70.31)	58.84(51.88,65.81)	63.77(59.68,67.86)	
Normal	63.08(61.44,64.72)	33.63(30.00,37.26)	36.26(29.69,42.83)	41.16(34.19,48.12)	36.23(32.14,40.32)	
PIR						<0.01
Low income	22.04(20.42,23.65)	16.37(13.61,19.13)	29.76(23.51,36.01)	22.45(16.84,28.06)	24.27(19.78,28.76)	
Middle income	35.83(34.13,37.52)	36.00(32.49,39.50)	36.22(30.28,42.16)	37.89(30.75,45.02)	36.74(32.08,41.40)	
Elevated income	42.14(39.89,44.38)	47.63(43.03,52.24)	34.02(27.68,40.36)	39.66(31.66,47.67)	38.98(32.91,45.05)	
Smoking						<0.01
Current	18.69(17.41,19.97)	18.21(15.47,20.95)	27.50(22.36,32.63)	27.31(21.50,33.12)	20.56(17.17,23.95)	
Before	21.77(20.30,23.24)	32.89(29.41,36.36)	33.14(26.79,39.49)	29.07(23.55,34.59)	34.03(30.01,38.05)	

Never	59.54(57.76,61.32)	48.90(45.48,52.32)	39.36(33.15,45.58)	43.62(37.28,49.96)	45.41(41.18,49.65)	
PAL						<0.01
Moderate activities	54.56(53.24,55.88)	73.88(70.67,77.08)	72.08(66.44,77.72)	67.01(59.61,74.40)	73.28(68.99,77.58)	
Vigorous activities	45.44(44.12,46.76)	26.12(22.92,29.33)	27.92(22.28,33.56)	32.99(25.60,40.39)	26.72(22.42,31.01)	
Diabetes						<0.01
Yes	8.50 (7.63,9.36)	15.81(13.36,18.27)	22.68(19.11,26.24)	16.27(10.90,21.63)	18.40(15.33,21.48)	
No	91.51(90.64,92.37)	84.19(81.73,86.64)	77.32(73.76,80.89)	83.73(78.37,89.10)	81.60(78.52,84.67)	
Uric acid						<0.01
AH	84.35(83.33,85.38)	84.18(81.78,86.59)	80.11(75.97,84.25)	84.42(79.68,89.17)	82.04(78.71,85.36)	
Normal state	15.65(14.62,16.67)	15.82(13.41,18.22)	19.88(15.75,24.03)	15.58(10.83,20.32)	17.96(14.64,21.29)	
Cholesterol(mg/dl) †	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
LDL (mg/dl) †	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
HDL (mg/dl) †	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
Triglycerides(mg/dl) †	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
Creatinine(mg/dl) †	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
Albumin(mg/L) †	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout);

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

Participants with OA are higher in non-Hispanic white (82.00% [95%CI: 79.15, 84.86]), hypertension (66.37% [62.74, 70.00]), elevated income (47.63% [43.03, 52.24]), moderate activities (73.88% [70.67, 77.08]), cholesterol (194.85±42.44) and HDL (57.40±36.73) than those without arthritis. Similar trends are observed in participants with RA, OA, other types of arthritis and those who responded with "don't know" when asked about the type of arthritis (Table 2).

And the proportion of participants who self-reported OA was the highest in arthritis. The proportion of AH is higher in participants with OA (84.18% [95%CI: 81.78, 85.59]) than in those with RA (80.11% [95%CI: 75.97, 84.25]) and unspecified (82.04% [95%CI: 78.71, 85.36]) arthritis types. But it is slightly lower than no arthritis (84.35% [95%CI: 83.33, 85.38]) and other arthritis (84.42% [95%CI; 79.68,89.17]) ($p<0.01$) (Table 2)

The association between AH and arthritis

Overall, AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07, 1.69) (Table 3). However, the association muted in different models after adjusting for demographic, socioeconomic factors, etc.

Table 3. Association between asymptomatic hyperuricemia and total arthritis.

	Unadjusted model	model 1	model 2	model 3
Control (Reference)	1	1	1	1
Total arthritis				
OR (95% CI)	1.34(1.07,1.69)	1.14(0.87,1.49)	1.11(0.83,1.48)	1.07(0.80,1.41)
P	0.012	<0.01	<0.01	<0.01

Model1: Adjusted for age, gender, and race.

Model2: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, diabetes, hypertension and smoking record.

Model3: Adjusted for age, gender, education level, income to poverty ratio, race, BMI, PAL, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine, and albumin.

For participants aged 40-49 years, AH is significantly associated with incident arthritis (OR=1.96, 95%CI: 1.23, 2.99). The association remained after adjusted for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.00, 95%CI: 1.94, 3.36) (Table 4).

Table 4. The total arthritis was analyzed stratified by gender, age, and race

	Model 1 (OR,95%, P)	Model 2 (OR,95%, P)	Model 3 (OR,95%,P)
Gander			
Male	1	1	1
Female	0.753(0.633,0.896)0.002	0.730 (0.608,0.877) 0.001	0.712(0.582,0.872)0.001
Age			
20-29	1	1	1
30-39	1.788(1.078,2.966)0.025	1.718(1.003,2.940)0.048	1.181(0.635,2.199)0.595
40-49	1.957(1.285,2.981)0.002	2.002(1.941,3.358)0.009	1.324(0.721,2.432)0.362
50-59	1.409(0.989,2.008)0.057	1.472(0.963,2.251)0.074	0.975(0.582,1.632)0.932
60-69	1.034(0.718,1.489)0.856	1.076(0.700,1.653)0.737	0.721(0.436,1.192)0.200
70+	1.106(0.789,1.549)0.556	1.122(0.725,1.737)0.602	0.739(0.426,1.282)0.278
Race			
Other Race	1	1	1
Hispanic	1.604(1.136,2.264)0.008	1.582(1.056,2.371)0.027	1.456(0.962,2.203)0.075
Non-Hispanic White	0.895(0.696,1.150)0.381	1.040(0.786,1.376)0.780	0.971(0.732,1.288)0.839
Non-Hispanic Black	2.017(1.471,2.765)0.000	2.305(1.622,3.276)0.000	2.203(1.536,3.160)0.000

Model1: Adjusted for age, gender, and race.

Model 2: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking record.

Model 3: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, hypertension, smoking, cholesterol, LDL, HDL, triglyceride, creatinine and albumin.

Among non-Hispanic black participants, AH was significantly associated with arthritis. (OR=2.02, 95%CI: 1.47, 2.77). The results kept significant adjusting for education level, income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.31, 95%CI: 1.62, 3.28) and for cholesterol, LDL, HDL, triglyceride, creatinine, and albumin (OR=2.20,95%CI: 1.55, 3.16) (Table 4).

Compared with male participants, female participants with AH showed a higher likelihood of OA (OR=1.35, 95%CI: 1.14, 1.60). However, for RA (OR: 1.08, 95%CI: 0.83, 1.41), other forms of arthritis (OR: 1.00, 95%CI: 0.78, 1.29), and the 'Unspecified' category (OR: 0.99, 95%CI: 0.82, 1.20), the observed associations were not statistically significant.

Notably, this trend was more prominent within the OA subgroup (sTable 2). Among participants aged > 50 years, there is a significant association between AH and different types of arthritis (including OA, RA, other, unspecified). More importantly, the strength of this association increased with age, specifically for 50-59 years, 60-69 years, 70+ years.

Discussion

Based on 12 years of nationally representative data from NHANES, our findings indicated an association between AH and the arthritis, with a notable focus on OA. The correlation was present before adjusting the model. However, after adjusting for additional variables such as cholesterol and creatinine, the correlation weakened, suggesting that the relationship between AH and arthritis (including OA) might not be independent and could be influenced by metabolic and physiological factors like cholesterol and creatinine[29]. Our research findings suggest a significant correlation between asymptomatic hyperuricemia (AH) and arthritis among non-Hispanic Black individuals, possibly due to metabolic syndrome-related metabolic abnormalities being less sensitive in identifying elevated uric acid levels in non-Hispanic Black populations [30].

Although hyperuricemia is a major contributor to the development of gouty arthritis, accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic arthritis and spondylarthritis[31-33]. In vitro studies on synoviocytes from healthy and RA subjects revealed that monosodium urate crystals could increase the release of the inflammatory cytokine IL-6, the chemokine CXCL8 and the matrix metalloproteinase-1[34]. The injection of urate crystals in vivo leads to produce main mediators in the pathogenesis of PsA, such as IL-17 [35]. The hyperuricemia not only play an important role the development and progression of psoriatic arthritis, but also affect severity of clinical manifestations and degree of inflammation[36]. Monosodium urate crystals interact with articular tissues to influence the development of axial spondyloarthritis as monosodium urate crystal deposition associated with the progress of radiographic grade at the sacroiliac joint[18, 37].

Our data indicate that AH may serve as a marker for potential risk in relation to OA. [22]. An increasing body of evidence suggests that AH, characterized by elevated serum uric acid levels without any symptoms of gout or kidney stone disease, may be associated with an increased risk of OA, particularly in weight-bearing joints such as the knee[16, 38,

39]. The relationship between AH and arthritis is complex and multifaceted, and the exact nature of this relationship is not yet clear. Hyperuricemia may promote the development of arthritis via deposition of urate crystals in the joints, promoting chronic low-grade inflammation, and exacerbating oxidative stress[20, 22, 40]. However, it is also possible that the association between hyperuricemia and arthritis is partially due to common risk factors such as obesity and metabolic syndrome[41, 42]. Further research is needed to better understand the relationship between these two conditions and to identify potential therapeutic targets for the prevention or treatment of arthritis in patients with hyperuricemia.

The intimate relationship between hyperuricemia and OA may re-purpose FDA-approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids[43]. However, these drugs could only use to relieve the clinical symptoms but not decrease the onset of arthritis. In accordance with our findings, another study also supports the significant association between arthritis and hypertension[44]. In recent years, there has been growing interest in exploring the role of urate-lowering therapy in the treatment of OA[45]. Urate crystal deposition can directly damage cartilage, stimulate the production of pro-inflammatory cytokines, and lead to inflammation and cartilage degradation[46]. Urate-lowering therapy drugs such as allopurinol and febuxostat have been shown to have anti-inflammatory properties, inhibit the production of reactive oxygen species, reduce the expression of pro-inflammatory cytokine[47-49]. Our results raise the possibility that pharmacological treatment of AH via a treat-to-target (T2T) strategy may decrease incident of arthritis, especially for OA. The T2T strategy involves targeting specific uric acid levels and adjusting drug therapy accordingly to achieve this goal[50, 51].

Our findings highlight those female participants with AH are more likely to develop arthritis, especially for OA, than male participants, and ageing may exaggerate this trend. Among adults in the US, serum urate was 6.0 mg/dl in men and 4.8 mg/dl in women, and hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[11]. Studies have also shown that hyperuricemia is more common in men over 30 and women over 50[52]. The gender and age associated increase in serum uric acid levels may be explained by menopause in women and alcohol consumption in men[53]. Menopause can lead to an

increase in serum uric acid levels, while postmenopausal hormone replacement therapy may be associated with a decrease in serum uric acid levels[54]. The difference in serum uric acid levels between men and women is due to the increased renal uric acid clearance caused by estrogen in women before menopause[55]. Serum Urate levels were significantly associated with knee OA as determined by osteophytosis in women but not in men[56]. Female typically have a higher prevalence of hand and knee arthritis than males, females also tend to have more severe knee OA, particularly after menopausal age[57].

The strength of our study was the use of data from a large, nationally representative sample. However, results should be interpreted with caution with inherent limitation. First, it is not possible to interpret the findings from a causal point of view due to the cross-sectional approach. Prospective study and mendelian randomization study are needed to further investigate the relationship between the AH and arthritis, especially OA. Second, recall bias may affect the accuracy of prevalence estimates although this study used CDC-recommended self-reported and physician-diagnosed arthritis as case definitions[24, 58]. Third, our result might be charged with choosing a single number to represent prevalent of arthritis in the US population as it only included adults in the national non-institutionalized population of the country[59]. Fourth, medication use for the participants was not included in this study. Finally, we had limited information on the involvement of OA in each participant, such as imaging and treatment procedures.

In summary, our study results suggest that AH patients may benefit from close monitoring for the development of arthritis, understanding the relationship between hyperuricemia and arthritis, and identifying factors that contribute to their increased risk of these diseases, which may be of great significance for the prevention and management of these conditions.

Contributors

Prof. Jieruo Gu is the guarantor of the study and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Zhenguo Liang, Dr. Dongze Wu, and Prof. Jieruo Gu, conceived and designed the study, performed the analysis, and wrote the paper. Prof. Hua Zhang participated in the revision and refinement of the content. All authors read and commented on the manuscript and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclaimer

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Declaration of interests

The authors declare no conflict of interests.

Ethical approval

The data released from the National Health and Nutrition Examination Survey did not require informed patient consent. This study used an anonymized publicly available data set with no identifiable information on the survey participants, and thus did not require ethics approval.

Data sharing

The data used for the analyses are publicly available from the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC) in the United States (https://www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

Supplemental appendix

sTable 1. Characteristics of participants included in this study.

sTable 2. Subgroup analysis of the association of arthritis subtype (RA, OA, other and unspecified) and AH.

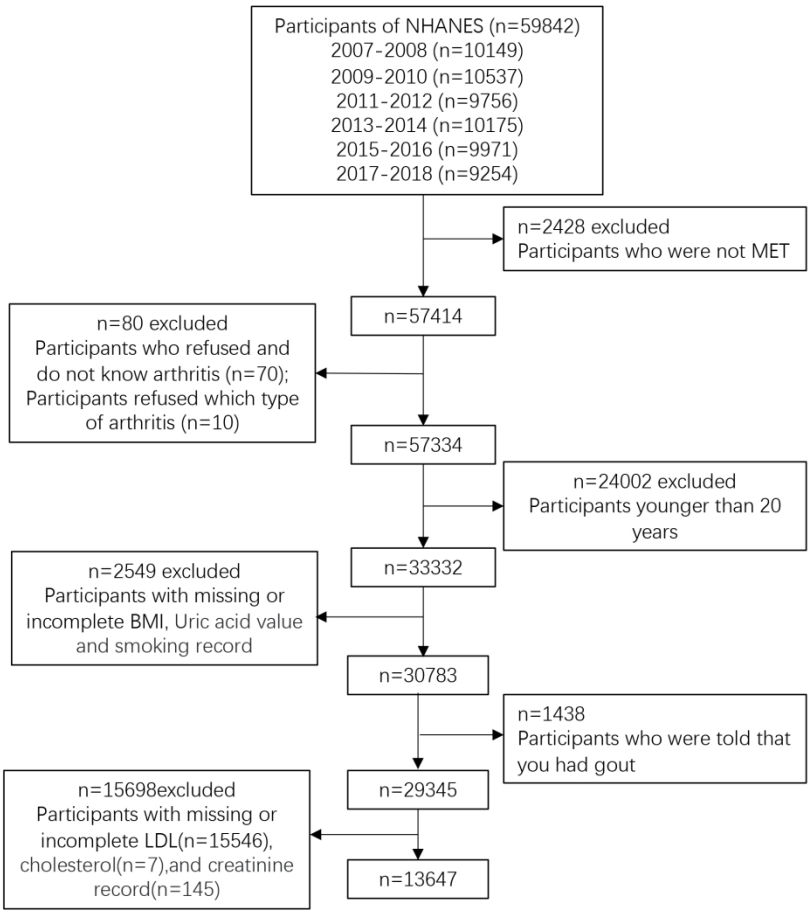

Figure 1. Flow chart of sample selection from the NHANES 2007–2018

188x175mm (300 x 300 DPI)

Supplementary materials

The association between asymptomatic hyperuricemia and risk of arthritis, findings from a US National Survey 2007-2018

Supplementary Tables

sTable1. Characteristics of participants included in this study

sTable2. Subgroup analysis of the association of arthritis subtype (RA, OA, Other and Unspecified) and AH.

Supplementary Table 1. Characteristics of participants included in this study

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	p
N*	2330	2528	2229	2367	2067	2126	
Uricacid							0.438
NA	83.65(81.60,85.69)	84.50(82.38,86.62)	84.71(82.87,86.64)	83.55(81.95,85.15)	84.13(82.09,86.17)	83.61(80.70,86.53)	
AH	16.35(14.01,18.40)	15.50(13.38,17.62)	15.29(13.46,17.13)	16.45(14.85,18.05)	15.87(13.83,17.91)	16.39(13.47,19.30)	
Gender							0.279
Male	47.25(45.60,48.89)	45.56(43.56,47.55)	47.90(45.04,50.75)	47.69(45.61,49.77)	47.36(45.31,49.42)	48.09(44.95,51.22)	
Female	52.75(51.11,54.40)	54.44(52.45,56.44)	52.10(49.25,54.96)	52.31(50.23,54.39)	52.64(50.58,54.69)	51.91(48.78,55.05)	
Age							<0.01
20-29	19.13(16.42,21.85)	19.35(16.80,21.90)	18.23(15.01,21.45)	18.40(15.73,21.08)	16.67(14.61,18.72)	19.86(16.81,22.90)	
30-39	18.20(15.96,20.43)	16.98(14.62,19.35)	18.53(15.67,21.39)	17.24(15.16,19.31)	15.59(14.04,17.15)	18.76(15.92,21.60)	
40-49	20.97(17.50,24.44)	21.50(19.52,23.49)	18.86(15.20,22.52)	19.43(16.80,22.07)	18.56(15.67,21.45)	15.71(13.13,18.28)	
50-59	19.29(16.77,21.80)	19.37(16.98,21.77)	19.08(17.07,21.08)	18.17(15.58,20.76)	18.81(17.09,20.54)	19.93(16.84,23.02)	
60-69	11.44(9.42,13.46)	11.18(9.90,12.46)	14.03(12.10,15.96)	14.71(12.03,17.38)	19.21(16.43,22.00)	14.81(11.45,18.16)	
70+	10.98(9.65,12.30)	11.60(10.10,13.10)	11.26(9.65,12.88)	12.05(10.37,13.73)	11.16(9.36,12.96)	10.95(8.93,12.97)	
Race/Ethnicity							<0.01
Other Race	13.87(10.43,17.31)	16.55(11.72,21.38)	15.80(11.44,20.16)	16.88(12.75,21.02)	17.24(13.58,20.90)	19.91(16.40,23.42)	
Hispanic	5.09(2.60,7.58)	5.84(2.94,8.74)	6.74(3.84,9.64)	5.67(2.34,8.61)	6.74(3.88,9.59)	6.86(5.00,8.72)	
Non-Hispanic White	70.37(63.63,77.11)	66.91(60.23,73.59)	68.04(61.22,74.87)	67.07(60.01,74.13)	65.74(57.81,73.66)	61.96(57.22,66.69)	

Non-Hispanic Black	10.67(6.63,14.70)	10.70(8.67,12.72)	9.42(5.94,12.90)	10.37(7.68,13.07)	10.29(5.86,14.71)	11.27(7.61,14.93)	
Education Level							<0.01
High school or below	43.02(37.88,48.16)	41.31(37.13,45.52)	37.42(31.97,42.87)	36.42(30.79,42.04)	36.46(30.23,42.68)	39.61(36.03,43.19)	
Some college	28.45(26.32,30.58)	29.63(26.71,32.56)	31.10(27.90,34.30)	32.90(29.91,35.90)	31.18(27.20,35.16)	29.91(25.07,34.76)	
College graduate or above	28.53(24.06,33.00)	29.05(25.76,32.33)	31.48(25.02,37.94)	30.68(26.29,35.07)	32.36(25.35,39.37)	30.47(24.72,36.23)	
BMI							<0.01
Normal	33.39(31.60,35.19)	32.13(28.74,35.52)	31.68(27.63,35.73)	31.24(28.78,33.70)	27.17(23.38,30.96)	29.29(25.52,33.05)	
Overweight	35.11(32.97,37.26)	32.96(30.44,35.48)	33.36(31.12,35.60)	33.31(30.91,35.70)	32.66(31.03,34.28)	31.53(29.18,33.8)	
Obesity	31.49(28.61,34.37)	34.91(32.02,37.79)	34.96(31.50,38.42)	35.45(33.20,37.70)	40.17(36.34,44.00)	39.18(35.37,43.00)	
Blood pressure							<0.01
Hypertension	40.92(37.47,44.37)	40.38(36.47,44.30)	45.82(41.97,49.68)	43.84(39.24,48.43)	44.44(40.49,48.40)	46.99(43.71,50.28)	
Normal	59.08(55.63,62.53)	59.62(55.70,63.53)	54.18(50.32,58.03)	56.16(51.57,60.76)	55.56(51.60,59.51)	53.01(49.72,56.29)	
PIR							<0.01
Low income	19.38(16.16,22.61)	21.90(19.24,24.56)	24.29(20.21,28.38)	25.33(19.07,31.59)	19.64(16.45,22.82)	20.01(17.46,22.56)	
Middle income	33.99(30.47,37.52)	37.50(33.75,41.26)	35.70(31.24,40.17)	33.69(30.70,36.68)	37.50(34.14,40.87)	37.61(33.36,41.86)	
High income	46.62(41.80,51.44)	40.60(36.83,44.36)	40.00(33.29,46.72)	40.98(34.20,47.76)	42.86(37.83,47.88)	42.38(37.89,46.88)	
Somking							0.01
Current	21.61(18.39,24.83)	18.98(17.51,20.45)	20.06(16.75,23.36)	19.50(15.86,23.14)	18.73(15.50,21.97)	17.47(14.68,20.27)	
Before	24.99(22.25,27.73)	24.21(20.55,27.87)	23.04(20.16,25.92)	23.68(20.64,26.72)	26.46(22.62,30.31)	24.90(22.47,27.32)	
Never	53.40(49.73,57.07)	56.80(53.00,60.61)	56.90(53.76,60.05)	56.82(52.86,60.78)	54.81(50.57,59.04)	57.63(54.64,60.62)	

PAL							<0.01
Moderate activities	58.98(55.40,62.57)	62.32(59.17,65.48)	61.71(57.96,65.46)	62.05(59.40,64.70)	57.56(54.23,60.90)	52.20(49.94,54.47)	
Vigorous activities	41.02(37.43,44.60)	37.68(34.52,40.83)	38.29(34.54,42.04)	37.95(35.30,40.60)	42.44(39.10,45.77)	47.80(45.53,50.06)	
Diabetes							<0.01
Yes	10.17(8.32,12.03)	9.47(8.21,10.74)	10.20(8.31,12.09)	10.34(8.83,11.84)	12.25(9.95,14.55)	12.14(9.78,14.49)	
No	89.83(87.97,91.68)	90.53(89.26,91.79)	89.80(87.91,91.69)	89.66(88.16,91.17)	87.75(85.45,90.05)	87.86(85.51,90.22)	
With or without arthritis							<0.01
No arthritis	74.05(70.64,77.47)	74.90(72.43,77.38)	77.19(73.85,80.53)	75.09(72.40,77.78)	73.16(70.09,76.24)	74.47(70.56,78.38)	
Arthritis	25.95(22.53,29.36)	25.10(22.62,27.57)	22.81(19.47,26.15)	24.91(22.22,27.60)	26.84(23.76,29.91)	25.53(21.62,29.44)	
OA	8.70(6.56,10.85)	9.56(8.30,10.82)	11.30(8.92,13.68)	13.88(11.87,15.89)	12.92(10.99,14.86)	12.44(9.32,15.55)	
RA	3.57(2.87,4.27)	4.11(3.18,5.04)	3.90(2.78,5.02)	3.09(2.15,4.02)	3.59(2.53,4.64)	4.04(2.82,5.25)	
Other	3.54(2.56,4.52)	3.64(2.80,4.47)	2.88(1.39,4.37)	2.98(2.05,3.91)	3.33(1.66,5.01)	3.04(1.78,4.30)	
Unspecified	10.13(8.22,12.05)	7.79(6.41,9.17)	4.73(3.14,6.33)	4.96(4.03,5.89)	6.99(5.25,8.73)	6.02(4.66,7.37)	
Cholesterol(mg/dl)†	194.90±40.98	195.00±39.66	191.78±39.95	188.44±39.94	190.31±41.06	186.04±40.55	<0.01
LDL(mg/dl)†	115.60±35.83	116.32±34.82	114.41±34.74	111.74±35.10	112.89±35.82	110.72±35.69	<0.01
HDL(mg/dl)†	54.15±15.40	54.40±15.95	53.78±14.93	54.58±16.11	55.97±17.56	54.02±15.74	<0.01
Triglyceride(mg/dl)†	125.72±66.36	121.43±64.17	117.95±64.42	110.61±65.08	107.26±63.05	106.48±63.30	<0.01
Creatinine(mg/dl)†	123.56±74.93	124.01±74.60	125.83±78.25	119.58±74.02	126.23±77.54	136.33±83.94	<0.01
Albumin(mg/dl)†	58.18±663.81	33.09±182.80	37.78±211.82	40.30±250.06	51.49±338.92	56.01±379.49	0.105

*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.

†Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL with no gout); NA: no-hyperuricemia.

Supplementary Table 2. Subgroup analysis of the association of arthritis subtype (RA, OA, Other and Unspecified) and AH

	OA (OR,95%, P)	RA (OR,95%, P)	Other (OR,95%, P)	Unspecified (OR,95%, P)
Gander				
Male	1	1	1	1
Female	1.35(1.14,1.60)0.00	1.08(0.83,1.41)0.59	1.00(0.78,1.29)1.00	0.99(0.82,1.20)0.96
Age				
20-29	1	1	1	1
30-39	0.36(0.27,0.49)0.00	0.36(0.24,0.54)0.00	0.35(0.23,0.55)0.00	0.38(0.27,0.53)0.00
40-49	0.80(0.62,1.04)0.97	0.99(0.71,1.38)0.96	0.88(0.64,1.21)0.44	0.95(0.70,1.30)0.74
50-59	2.16(1.72,2.72)0.00	2.12(1.50,3.00)0.000	1.35(1.00,1.83)0.51	1.90(1.44,2.49)0.00
60-69	4.18(3.26,5.35)0.00	3.34(2.50,4.46)0.000	1.69(1.13,2.53)0.01	2.70(1.92,3.78)0.00
70+	5.50(4.18,7.22)0.00	4.57(3.40,6.15)0.000	1.51(0.99,2.33)0.06	4.24(3.16,5.69)0.00

RA: rheumatoid arthritis; OA: osteoarthritis; AH: asymptomatic hyperuricemia

All data were adjusted for gender, age, race, BMI, education level and poverty to income ratio, hypertension, ever cigarette smoking and diabetes.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 13-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.