

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-074391
Article Type:	Original research
Date Submitted by the Author:	04-Apr-2023
Complete List of Authors:	Liang, Zhenguo; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology WU, Dongze; University of Electronic Science and Technology of China Sichuan Provincial People's Hospital, Department of Rheumatology and Immunology; Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital Gu, Jieruo; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology
Keywords:	Rheumatology < INTERNAL MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

3  
4 **Author**

5 Zhenguo Liang<sup>1#</sup>, Dongze Wu<sup>2,3#</sup>, Jieruo Gu<sup>1\*</sup>

6 **Institution**

7 1.Department of Rheumatology, Third Affiliated Hospital of Sun Yat-Sen University,  
8 Guangzhou, Guangdong, China.

9 2.Department of Rheumatology and Immunology, Sichuan Provincial People's Hospital,  
10 University of Electronic Science and Technology of China, Chengdu, China.

11 3.Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital,  
12 Chengdu, China.

13 #Contributed equally to this manuscript.

14 **Corresponding authors**

15 \*Prof. Jieguo Gu, PhD

16 Address: No. 600 Tianhe Road, Tianhe District, Guangzhou, Guangdong, China, 510000

17 E-mail: gujieruo@mail.sysu.edu.cn

18 Telephone: (+86) 2085253333 / Fax number: (+86) 2085253336

19 **Word Count: 2980**      **Table Count: 4**      **Figure Count:1**

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

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

## 22 Abstract

### 23 Background

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

### 26 Methods

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

### 33 Result

34 During the past 12 years, the percentage of participants with arthritis changed from  
35 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA)  
36 increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence  
37 of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30).  
38 Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69),  
39 but the association was muted after adjusting demographic, socioeconomic factors, etc. For  
40 participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI:  
41 1.23, 2.99) and the relationship remained after adjusting for education level, income to  
42 poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00,  
43 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to  
44 develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

### 45 Conclusion

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

49 **Keywords:** Arthritis, Asymptomatic hyperuricemia, Association, Risk

## 51 **What is already known about this subject**

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

## 55 **What does this study add**

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

## 58 **How might this impact on clinical practice**

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

## 62 **Introduction**

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

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

1  
2  
3 82 approximately 15–40% of patients with chronic hyperuricemia have silent monosodium  
4 83 urate crystal deposition[12]. As crystallization of monosodium urate is the turning point of  
5  
6 84 hyperuricemia progress towards gout, whether hyperuricemia contribute to other arthritis  
7  
8 85 remain uncertain[13].  
9

10 86 Hyperuricemia and OA separately driven by common risk factors such as obesity and  
11 87 aging, intraarticular urate result in urate crystallization and deposition on the cartilage,  
12 88 disruption of cartilage by promotes urate crystallization and deposition[14]. The  
13  
14 89 predilection for both OA and gout occur in the same joints strongly suggest that OA may  
15 90 predispose to the localized deposition of monosodium urate crystals, which influence  
16  
17 91 structural joint damage[15-17]. Monosodium urate crystals have been shown to inhibit the  
18 92 viability and function of human chondrocytes in vitro with a dose-dependent manner[18].  
19  
20 93 Death of chondrocytes can lead to an increase in urate, which may even promote crystal  
21  
22 94 deposition on the cartilage, further aggravating OA progression[14]. Monosodium urate  
23  
24 95 crystals inhibit osteocyte viability and, through interactions with macrophages, indirectly  
25 96 promote a shift in osteocyte function that favors bone resorption and inflammation[19].  
26  
27 97 Uric acid is a danger signal of increasing risk OA through inflammasome activation[20].  
28  
29 98 Therefore, we hypothesized that hyperuricemia prior to gout was associated with OA. The  
30  
31 99 aim of this study was to i) ascertain the association between AH and arthritis, ii) determine  
32  
33 100 the association between AH and OA, iii) investigate the effect of age and gender on such  
34  
35 101 association.  
36

## 37 102 **Patients and methods**

### 38 103 **Study population**

39 104 NHANES is an ongoing longitudinal survey conducted by the National Center for  
40  
41 105 Health Statistics (NCHS) to assess the health and nutritional status of the United States  
42  
43 106 through a series of interviews and examination items. The NHANES is conducted  
44  
45 107 biennially in a nationally representative, non-institutionalized civilian population, and use  
46  
47 108 a hierarchical multi-stage probabilistic clustering design to select a representative sample  
48  
49 109 of over-sampled participants. The sampling methods and examination information used in  
50  
51 110 this study have been described in detail elsewhere[21]. NHANES was reviewed and  
52  
53 111 approved by the NCHS Research Ethics Committee. All manipulations of the NHANES  
54  
55 112 were carried out in accordance with the principles of the Helsinki Declaration. Written  
56  
57  
58  
59  
60

1  
2  
3 113 informed consent was obtained from all participants in NHANES.  
4

5 114 The study used data from NHANES database for the 2007-2018 study cycle  
6 115 (n=59,842) and excluded those who did not participate in the examination (n=2,428). We  
7 116 excluded participants who refused and don't know ever had or hadn't arthritis, refused to  
8 117 answer which type of arthritis (n=80), who are younger than 20 years old (n=24,002), who  
9 118 have missing and incomplete BMI, uric value, and smoking record (n=6,799). We also  
10 119 excluded participants who were told that you had gout(n=1,438) and participants with  
11 120 missing or incomplete low-density lipoprotein (LDL), cholesterol, and creatinine record.  
12 121 In the end, this study consisted of 13, 647 eligible participants (Figure 1), which is  
13 122 representative of the population size of 87,901,487.  
14  
15  
16  
17  
18  
19

### 20 123 **Conditions of arthritis**

21  
22 124 The status of arthritis was classified using questionnaires. Participants aged 20 years  
23 125 and older were asked "Has a doctor or other health professional ever said that you had  
24 126 arthritis?". If the participants gave a positive answer, they were further asked "Which type  
25 127 of arthritis was it?". Participants' responses included rheumatoid arthritis (RA), OA, other,  
26 128 do not know type, and refuse to answer. Individuals were excluded from the current  
27 129 analysis if their self-reported type of arthritis declined to answer. A consistent relationship  
28 130 between self-reports of arthritis and a clinical diagnosis of arthritis has been demonstrated  
29 131 in previous reports[22].  
30  
31  
32  
33  
34  
35

### 36 132 **Hyperuricemia**

37 133 Hyperuricemia is an elevated level of uric acid in the blood. The normal upper limit for  
38 134 serum uric acid (SUA) at physiological levels is 6.8 mg/dL. This is the saturation point at  
39 135 which urate may precipitate under physiological conditions[23]. We put  $SUA > 6.8$  mg/dL  
40 136 was defined as hyperuricemia, and  $SUA \leq 6.8$  mg/dL is defined as the normal state.  
41  
42  
43  
44

### 45 137 **Covariates**

46 138 Covariates are identified in statistical models by means of interview responses and  
47 139 examinations. Covariates were selected based on the results of interviews and examinations  
48 140 in the NHANES database to screen for factors that may be associated with OA risk and/or  
49 141 may be associated with AH, which could confound the association between OA and AH.  
50 142 Based on self-reported demographic characteristics, including gender, age, race/, education  
51 143 level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 144 (PAL), diabetes.

4  
5 145 Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race/ is  
6  
7 146 divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other  
8  
9 147 races. Education is grouped as high school or below, some college and college graduate or  
10  
11 148 above. BMI is calculated from measured weight and height determined by standard  
12  
13 149 NHANES protocols[24]. BMI is categorized as three groups: Normal ( $<18.5\text{kg/m}^2$ ),  
14  
15 150 Overweight ( $18.5\text{--}24.9\text{kg/m}^2$ ) and Obesity ( $\geq 25\text{kg/m}^2$ ). Participants with systolic blood  
16  
17 151 pressure  $\geq 130\text{mmHg}$  or diastolic blood pressure  $\geq 80\text{mmHg}$  are defined as  
18  
19 152 hypertension[25]. PIR as a socioeconomic indicator are stratified into three levels: Low  
20  
21 153 income ( $\text{PIR} < 1.3$ ), Middle income ( $1.3 \leq \text{PIR} < 3.5$ ) and High income ( $\text{PIR} \geq 3.5$ ).

22  
23 154 Smoking status is categorized according to interview results as current (smoked more  
24  
25 155 than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than  
26  
27 156 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100  
28  
29 157 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which  
30  
31 158 includes moderate work activity, walking or cycling, moderate recreational activity, and  
32  
33 159 vigorous activity, which includes vigorous work activity and vigorous recreational activity.  
34  
35 160 Participants with self-reported diabetes had either a diabetes physician's diagnosis of  
36  
37 161 diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance  
38  
39 162 (OGTT), or/and  $\text{HbA1c} \geq 6.5\%$ . Laboratory data included cholesterol, LDL, High-density  
40  
41 163 lipoprotein (HDL), triglycerides, creatinine, and albumin.

#### 42 164 **Statistical analysis**

43  
44 165 Design factors involving complex weighting, clustering, and stratification in the  
45  
46 166 NHANES database. Statistical analysis was conducted using STATA (version 16).  
47  
48 167 Complex stratification designs were considered using appropriate sample weights in  
49  
50 168 accordance with NHANES analytical reporting guidelines. In baseline study characteristics,  
51  
52 169 means and standard errors (SEs) were used for continuous variables. Categorical variables  
53  
54 170 were expressed as numbers and percentages. Chi-square test and t-test were used for  
55  
56 171 categorical and continuous variables, respectively. A weighted logistic regression was used  
57  
58 172 to assess the association between OA and AH and to control for confounding factors.  
59  
60 173 Finally, subgroup analysis was performed using hierarchical multivariate regression. The  
174  
95% confidence intervals and p-values were calculated. A two-tailed test with p-values less

1  
2  
3 175 than 0.05 are considered significant.  
4

## 5 176 **Results**

### 6 177 **The characteristics of study participants**

7  
8 178 A total of 13,647 participants were eligible and included in the analysis from 2007-2008  
9  
10 179 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of  
11  
12 180 participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81%  
13  
14 181 (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09%  
15  
16 182 (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic  
17  
18 183 whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69).  
19  
20 184 Between 2007-2008 and 2017-2018, the proportion of high school or below decreased,  
21  
22 185 which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the  
23  
24 186 proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06,  
25  
26 187 33.00) to 30.47% (95%CI: 24.72, 36.23) .

27 188 During the past 12 years, the percentage of participants with arthritis changed from  
28  
29 189 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from  
30  
31 190 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while  
32  
33 191 the proportion of those who don't know arthritis decreased from 10.13% (95%CI:  
34  
35 192 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis  
36  
37 193 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed  
38  
39 194 a clear upward trend during the 12 years, from 8.70% (95%CI: 6.56, 10.85) in 2007-2008  
40  
41 195 to 12.44% (95%CI: 9.32, 15.55) in 2017-2018 (p<0.01).

42 196 In all age groups, the highest proportion of individuals with AH was observed in the 50-  
43  
44 197 59 age group. (19.39% [95%CI: 17.17, 21.61]). A larger proportion of males (77.17%  
45  
46 198 [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI: 20.63, 25.04])  
47  
48 199 (Table 2). There are significant differences in race between participants with and without  
49  
50 200 AH (p<0.01). Participants in the AH group had higher levels of obesity, hypertension,  
51  
52 201 diabetes, LDL, triglycerides, and creatinine than those in the healthy control group.

53 202 The prevalence of patients with osteoarthritic and AH (11.40% [95%CI: 9.56, 13.24])  
54  
55 203 is considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56,  
56  
57 204 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and don't know: 7.54% (95%CI: 6.03, 9.05))  
58  
59 205 (p<0.01).  
60

1  
2  
3 206 **The characteristics of hyperuricemia and arthritis**  
4

5 207 Participants with arthritis, including OA, RA, other and don't know of arthritis, were  
6  
7 208 more frequent in people aged over 50 years than those without arthritis (Table 1). The  
8  
9 209 characteristics of the 13,647 participants included in our study with self-reported OA, RA,  
10  
11 210 other, and don't know are presented using weighted statistics (Table 2). The prevalence of  
12  
13 211 the four types of arthritis was higher among female participants than among male  
14  
15 212 participants, which was most notable in OA (female: 65.94% vs male 30.06%).  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

Characteristics	No Arthritis	OA	RA	Other	Don't know	p value
<b>N*</b>	10089	1402	662	408	1086	
<b>Gender</b>						<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)	
<b>Age</b>						<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)	
<b>Race</b>						<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)	
<b>Education Level</b>						<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)	
<b>BMI</b>						<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)	

1							
2							
3							
4							
5	<b>Blood pressure</b>						<0.01
6	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)	
7	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)	
8							
9	<b>PIR</b>						<0.01
10	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)	
11	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)	
12	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)	
13							
14	<b>Smoking</b>						<0.01
15	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)	
16	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)	
17	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)	
18							
19	<b>PAL</b>						<0.01
20	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)	
21	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)	
22							
23	<b>Diabetes</b>						<0.01
24	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)	
25	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)	
26							
27							
28	<b>Uric acid</b>						<0.01
29	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)	
30	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)	
31							
32	<b>Cholesterol(mg/dl) †</b>	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
33	<b>LDL (mg/dl) †</b>	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
34	<b>HDL (mg/dl) †</b>	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
35	<b>Triglycerides(mg/dl) †</b>	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
36	<b>Creatinine(mg/dl) †</b>	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
37	<b>Albumin(mg/L) †</b>	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1  
2  
3  
4  
5 214 BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL: High-density  
6 215 lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate > 6.8 mg/dL without gout);  
7  
8 216 \*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination weight.  
9  
10 217 †Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).  
11  
12 218

For peer review only

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

Characteristics	Healthy control	AH	p value
<b>N*</b>	11387	2260	
<b>Gender</b>			<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)	
<b>Age</b>			<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)	
<b>Race</b>			<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)	
<b>Education Level</b>			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)	
<b>BMI</b>			<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)	
<b>Blood pressure</b>			<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)	
<b>PIR</b>			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)	
<b>Smoking</b>			<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)	
<b>PAL</b>			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)	
<b>Diabetes</b>			<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)	
<b>Arthritis</b>			<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)	
<b>Cholesterol(mg/dl) †</b>	191.01±40.22	192.23±41.65	0.1924
<b>LDL (mg/dl)†</b>	113.39±35.07	115.48±36.82	0.0088
<b>HDL (mg/dl)†</b>	55.58±15.89	48.87±15.10	<0.01
<b>Triglycerides(mg/dl) †</b>	110.45±62.12	139.39±73.24	<0.01
<b>Creatinine(mg/dl)†</b>	122.00±75.58	144.47±82.80	<0.01
<b>Albumin(mg/dl)†</b>	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 ( $194.85\pm 42.44$ ) and HDL ( $57.40\pm 36.73$ ) 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
<b>Osteoarthritis</b>				
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)
<b>Gander</b>			
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
<b>Age</b>			
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
<b>Race</b>			
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

1  
2  
3 association between hyperuricemia and arthritis is partially due to common risk factors  
4 such as obesity and metabolic syndrome[34, 35]. Further research is needed to better  
5 understand the relationship between these two conditions and to identify potential  
6 therapeutic targets for the prevention or treatment of arthritis in patients with  
7 hyperuricemia.  
8  
9

10  
11 The intimate relationship between hyperuricemia and OA may re-purpose FDA-  
12 approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used  
13 to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs),  
14 corticosteroids, and opioids[36]. However, these drugs could only used to relieve the  
15 clinical symptoms but not decrease the onset of arthritis. In recent years, there has been  
16 growing interest in exploring the role of urate-lowering therapy in the treatment of OA[37].  
17 Urate crystal deposition can directly damage cartilage, stimulate the production of pro-  
18 inflammatory cytokines, and lead to inflammation and cartilage degradation[38]. Urate-  
19 lowering therapy drugs such as allopurinol and febuxostat have been shown to have anti-  
20 inflammatory properties, inhibit the production of reactive oxygen species, reduce the  
21 expression of pro-inflammatory cytokine[39-41]. Our results also suggest pharmacological  
22 treatment of AH via a treat-to-target (T2T) strategy may decrease incident of arthritis,  
23 especially for OA. The T2T strategy involves targeting specific uric acid levels and  
24 adjusting drug therapy accordingly to achieve this goal[42, 43].  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

36 Our findings highlight those female participants with AH are more likely to develop  
37 arthritis, especially for OA, than male participants, and ageing may exaggerate this trend.  
38 Among adults in the US, mean serum urate levels were 6.0 mg/dl in men and 4.8 mg/dl in  
39 women, and hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[9].  
40 Studies have also shown that hyperuricemia is more common in men over 30 and women  
41 over 50[44]. The gender and age associated increase in serum uric acid levels may be  
42 explained by menopause in women and alcohol consumption in men[45]. Menopause can  
43 lead to an increase in serum uric acid levels, while postmenopausal hormone replacement  
44 therapy may be associated with a decrease in serum uric acid levels[46]. The difference in  
45 serum uric acid levels between men and women is due to the increased renal uric acid  
46 clearance caused by estrogen in women before menopause[47]. When osteophytes were  
47 present, blood uric acid levels were significantly elevated in women with OA, but this was  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 not observed in men with OA[48]. Female typically have a higher prevalence of hand and  
4 knee arthritis than males, females also tend to have more severe knee OA, particularly after  
5 menopausal age[49].  
6  
7

8 The strength of our study was the use of data from a large, nationally representative  
9 sample. However, results should be interpreted with caution with inherent limitation. First,  
10 it is not possible to interpret the findings from a causal point of view due to the cross-  
11 sectional approach. Prospective study and mendelian randomization study are needed to  
12 further investigate the relationship between the AH and arthritis, especially OA. Second,  
13 recall bias may affect the accuracy of prevalence estimates although this study used CDC-  
14 recommended self-reported and physician-diagnosed arthritis as case definitions[22, 50].  
15 Third, our result might be charged with choosing a single number to represent prevalent of  
16 arthritis in the US population as it only included adults in the national non-institutionalized  
17 population of the country[51]. Fourth, medication use for the participants was not included  
18 in this study. Finally, we had limited information on the involvement of OA in each  
19 participant, such as imaging and treatment procedures.  
20  
21  
22  
23  
24  
25  
26  
27  
28

29 In summary, our study results suggest that AH patients may benefit from close  
30 monitoring for the development of arthritis, understanding the relationship between  
31 hyperuricemia and arthritis, and identifying factors that contribute to their increased risk  
32 of these diseases, which may be of great significance for the prevention and management  
33 of these conditions.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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.

## Funding

Project funded by Guangdong Clinical Research Center of Immune Disease (2020B1111170008) & Scientific Research Fund of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (2022QN38).

## Disclaimer

The funder was not involved in the preparation of this manuscript.

## 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/>).

## Reference

1. Barbour, K.E., et al., *Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation - United States, 2013-2015*. MMWR Morb Mortal Wkly Rep, 2017. **66**(9): p. 246-253.
2. Hootman, J.M., et al., *Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040*. Arthritis Rheumatol, 2016. **68**(7): p. 1582-7.
3. Murphy, L.B., et al., *Medical Expenditures and Earnings Losses Among US Adults With Arthritis in 2013*. Arthritis Care Res (Hoboken), 2018. **70**(6): p. 869-876.
4. Hunter, D.J. and S. Bierma-Zeinstra, *Osteoarthritis*. Lancet, 2019. **393**(10182): p. 1745-1759.
5. *Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019*. Lancet, 2020. **396**(10258): p. 1204-1222.
6. Partridge, L., J. Deelen, and P.E. Slagboom, *Facing up to the global challenges of ageing*. Nature, 2018. **561**(7721): p. 45-56.
7. Bortoluzzi, A., F. Furini, and C.A. Scirè, *Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors*. Autoimmun Rev, 2018. **17**(11): p. 1097-1104.
8. Mobasheri, A., et al., *The role of metabolism in the pathogenesis of osteoarthritis*. Nat Rev Rheumatol, 2017. **13**(5): p. 302-311.
9. Chen-Xu, M., et al., *Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007-2016*. Arthritis Rheumatol, 2019. **71**(6): p. 991-999.
10. Dalbeth, N., et al., *Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis*. Ann Rheum Dis, 2018. **77**(7): p. 1048-1052.
11. Lioté, F. and T. Pascart, *From hyperuricaemia to gout: what are the missing links?* Nat Rev Rheumatol, 2018. **14**(8): p. 448-449.
12. Dalbeth, N. and L. Stamp, *Hyperuricaemia and gout: time for a new staging system?* Ann Rheum Dis, 2014. **73**(9): p. 1598-600.
13. Dalbeth, N., et al., *Gout*. Lancet, 2021. **397**(10287): p. 1843-1855.
14. Neogi, T., S. Krasnokutsky, and M.H. Pillinger, *Urate and osteoarthritis: Evidence for a reciprocal relationship*. Joint Bone Spine, 2019. **86**(5): p. 576-582.
15. Roddy, E., W. Zhang, and M. Doherty, *Are joints affected by gout also affected by osteoarthritis?* Ann Rheum Dis, 2007. **66**(10): p. 1374-7.

16. Dalbeth, N., et al., *Relationship between structural joint damage and urate deposition in gout: a plain radiography and dual-energy CT study*. Ann Rheum Dis, 2015. **74**(6): p. 1030-6.
17. Yokose, C., et al., *Gout and Osteoarthritis: Associations, Pathophysiology, and Therapeutic Implications*. Curr Rheumatol Rep, 2016. **18**(10): p. 65.
18. Chhana, A., et al., *The effects of monosodium urate monohydrate crystals on chondrocyte viability and function: implications for development of cartilage damage in gout*. J Rheumatol, 2013. **40**(12): p. 2067-74.
19. Chhana, A., et al., *Monosodium urate crystals reduce osteocyte viability and indirectly promote a shift in osteocyte function towards a proinflammatory and proresorptive state*. Arthritis Res Ther, 2018. **20**(1): p. 208.
20. Denoble, A.E., et al., *Uric acid is a danger signal of increasing risk for osteoarthritis through inflammasome activation*. Proc Natl Acad Sci U S A, 2011. **108**(5): p. 2088-93.
21. Zhu, Z., et al., *The Association between Retinopathy and Arthritis: Findings from a US National Survey 2005-2008*. Curr Eye Res, 2020. **45**(12): p. 1543-1549.
22. March, L.M., et al., *Clinical validation of self-reported osteoarthritis*. Osteoarthritis Cartilage, 1998. **6**(2): p. 87-93.
23. Martillo, M.A., L. Nazzari, and D.B. Crittenden, *The crystallization of monosodium urate*. Curr Rheumatol Rep, 2014. **16**(2): p. 400.
24. *Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures*. Vital Health Stat 1, 1994(32): p. 1-407.
25. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines*. Hypertension, 2018. **71**(6): p. 1269-1324.
26. Kuo, C.F., et al., *Global epidemiology of gout: prevalence, incidence and risk factors*. Nat Rev Rheumatol, 2015. **11**(11): p. 649-62.
27. Chen, D.P., et al., *Activation of human fibroblast-like synoviocytes by uric acid crystals in rheumatoid arthritis*. Cell Mol Immunol, 2011. **8**(6): p. 469-78.
28. Raucchi, F., et al., *IL-17A neutralizing antibody regulates monosodium urate crystal-induced gouty inflammation*. Pharmacol Res, 2019. **147**: p. 104351.
29. Tripolino, C., et al., *Hyperuricemia in Psoriatic Arthritis: Epidemiology, Pathophysiology, and Clinical Implications*. Front Med (Lausanne), 2021. **8**: p. 737573.
30. Zhu, J., et al., *Monosodium urate crystal deposition associated with the progress of radiographic grade at the sacroiliac joint in axial SpA: a dual-energy CT study*. Arthritis Res



- 1  
2  
3  
4 Ther, 2017. **19**(1): p. 83.
- 5 31. Wang, S., et al., *The association between asymptomatic hyperuricemia and knee*  
6 *osteoarthritis: data from the third National Health and Nutrition Examination Survey.*  
7 *Osteoarthritis Cartilage*, 2019. **27**(9): p. 1301-1308.
- 8 32. Xiao, L., S. Lin, and F. Zhan, *The association between serum uric acid level and changes*  
9 *of MRI findings in knee osteoarthritis: A retrospective study (A STROBE-compliant article).*  
10 *Medicine (Baltimore)*, 2019. **98**(21): p. e15819.
- 11 33. Joosten, L.A.B., et al., *Asymptomatic hyperuricaemia: a silent activator of the innate*  
12 *immune system.* *Nat Rev Rheumatol*, 2020. **16**(2): p. 75-86.
- 13 34. Zurita-Cruz, J., et al., *Resistin/Uric Acid Index as a Prognostic Factor in Adolescents with*  
14 *Obesity after Lifestyle Intervention.* *J Pediatr*, 2020. **219**: p. 38-42.e1.
- 15 35. Musumeci, G., et al., *Osteoarthritis in the XXIst century: risk factors and behaviours that*  
16 *influence disease onset and progression.* *Int J Mol Sci*, 2015. **16**(3): p. 6093-112.
- 17 36. Zhang, Y., et al., *Low-dose aspirin use and recurrent gout attacks.* *Ann Rheum Dis*, 2014.  
18 **73**(2): p. 385-90.
- 19 37. Bardin, T. and P. Richette, *Impact of comorbidities on gout and hyperuricaemia: an update*  
20 *on prevalence and treatment options.* *BMC Med*, 2017. **15**(1): p. 123.
- 21 38. Schett, G., et al., *Why does the gout attack stop? A roadmap for the immune pathogenesis*  
22 *of gout.* *RMD Open*, 2015. **1**(Suppl 1): p. e000046.
- 23 39. Geng, Q., et al., *Febuxostat mitigates IL-18-induced inflammatory response and reduction*  
24 *of extracellular matrix gene.* *Am J Transl Res*, 2021. **13**(3): p. 979-987.
- 25 40. Nasi, S., et al., *Xanthine Oxidoreductase Is Involved in Chondrocyte Mineralization and*  
26 *Expressed in Osteoarthritic Damaged Cartilage.* *Front Cell Dev Biol*, 2021. **9**: p. 612440.
- 27 41. Li, J., Z. Zhang, and X. Huang, *L-Arginine and allopurinol supplementation attenuates*  
28 *inflammatory mediators in human osteoblasts-osteoarthritis cells.* *Int J Biol Macromol*, 2018.  
29 **118**(Pt A): p. 716-721.
- 30 42. Kiltz, U., et al., *Treat-to-target (T2T) recommendations for gout.* *Ann Rheum Dis*, 2017.  
31 **76**(4): p. 632-638.
- 32 43. Perez-Ruiz, F., et al., *Treat to target in gout.* *Rheumatology (Oxford)*, 2018. **57**(suppl\_1):  
33 p. i20-i26.
- 34 44. Miao, Z., et al., *Dietary and lifestyle changes associated with high prevalence of*  
35 *hyperuricemia and gout in the Shandong coastal cities of Eastern China.* *J Rheumatol*,  
36 2008. **35**(9): p. 1859-64.
- 37 45. Lin, K.C., H.Y. Lin, and P. Chou, *The interaction between uric acid level and other risk*  
38 *factors on the development of gout among asymptomatic hyperuricemic men in a*  
39 *prospective study.* *J Rheumatol*, 2000. **27**(6): p. 1501-5.
- 40 46. Hak, A.E. and H.K. Choi, *Menopause, postmenopausal hormone use and serum uric acid*  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- levels in US women--the Third National Health and Nutrition Examination Survey. Arthritis Res Ther, 2008. 10(5): p. R116.*
47. Nicholls, A., M.L. Snaith, and J.T. Scott, *Effect of oestrogen therapy on plasma and urinary levels of uric acid. Br Med J, 1973. 1(5851): p. 449-51.*
48. Ding, X., et al., *The associations of serum uric acid level and hyperuricemia with knee osteoarthritis. Rheumatol Int, 2016. 36(4): p. 567-73.*
49. Srikanth, V.K., et al., *A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage, 2005. 13(9): p. 769-81.*
50. El Miedany, Y., et al., *Incorporating patient reported outcome measures in clinical practice: development and validation of a questionnaire for inflammatory arthritis. Clin Exp Rheumatol, 2010. 28(5): p. 734-44.*
51. Murphy, L.B., et al., *Defining Arthritis for Public Health Surveillance: Methods and Estimates in Four US Population Health Surveys. Arthritis Care Res (Hoboken), 2017. 69(3): p. 356-367.*

**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.

For peer review only

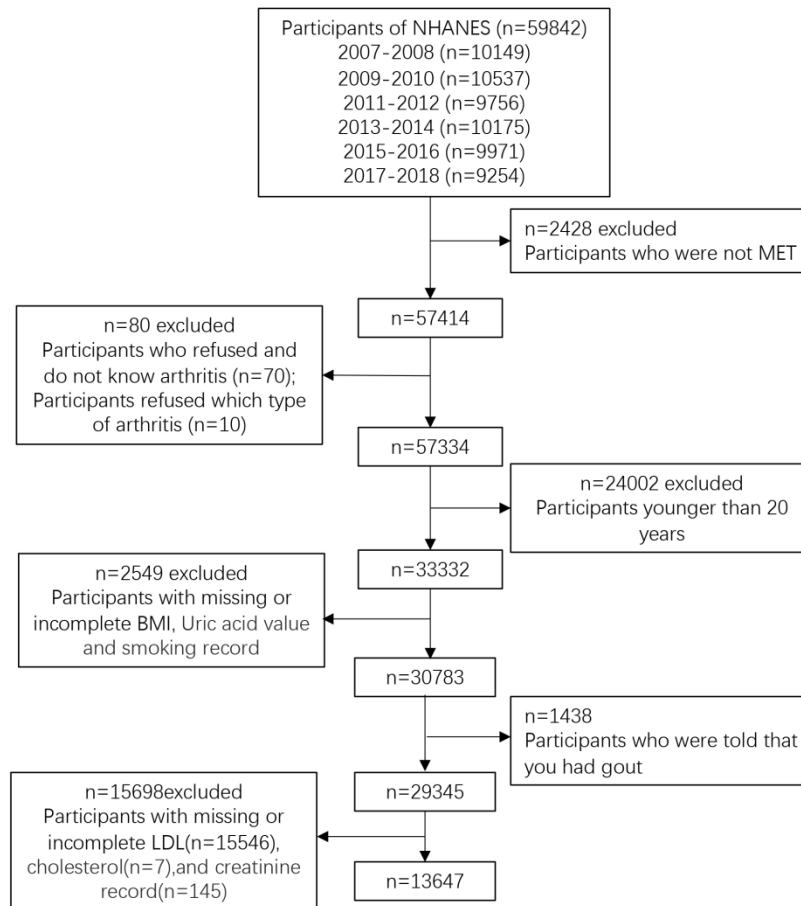


Figure 1. Flow chart of sample selection from the NHANES 2007–2018

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
<b>N*</b>	2330	2528	2229	2367	2067	2126	
<b>Uricacid</b>							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)	
<b>Gender</b>							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)	
<b>Age</b>							<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)	
<b>Race/Ethnicity</b>							<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)	

1							
2							
3							
4							
5	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)
6							
7	<b>Education Level</b>						<0.01
8	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)
9	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)
10	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)
11							
12							
13	<b>BMI</b>						<0.01
14							
15	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)
16	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)
17	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)
18							
19							
20	<b>Blood pressure</b>						<0.01
21	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)
22	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)
23							
24							
25	<b>PIR</b>						<0.01
26	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)
27	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)
28	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)
29							
30							
31	<b>Smoking</b>						0.01
32	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)
33	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)
34	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)
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							

<b>PAL</b>								<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)		
<b>Diabetes</b>								<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)		
<b>With or without arthritis</b>								<0.01
<b>No arthritis</b>	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)		
<b>Arthritis</b>	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)		
<b>Cholesterol(mg/dl)†</b>	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
<b>LDL(mg/dl)†</b>	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
<b>HDL(mg/dl)†</b>	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
<b>Triglyceride(mg/dl)†</b>	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
<b>Creatinine(mg/dl)†</b>	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
<b>Albumin(mg/dl)†</b>	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).



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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)
<b>Gander</b>				
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
<b>Age</b>				
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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

1	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	13-14
2		(b) Report category boundaries when continuous variables were categorized		
3		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
5	<b>Discussion</b>			
6	Key results	18	Summarise key results with reference to study objectives	15-16
7	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
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	
10	<b>Other information</b>			
11	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>.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-074391.R1
Article Type:	Original research
Date Submitted by the Author:	14-Nov-2023
Complete List of Authors:	Liang, Zhenguo; The Fifth Affiliated Hospital of Sun Yat-sen University, Department of Rheumatology and Immunology; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology WU, Dongze; University of Electronic Science and Technology of China Sichuan Provincial People's Hospital, Department of Rheumatology and Immunology; Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital Zhang, Hua; The Fifth Affiliated Hospital of Sun Yat-sen University, Department of Rheumatology and Immunology Gu, Jieruo; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology
<b>Primary Subject Heading</b>:	Immunology (including allergy)
Secondary Subject Heading:	Complementary medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 1 **The association between asymptomatic hyperuricemia and risk of arthritis, findings**  
4 **from a US National Survey 2007-2018**  
5  
6

7 3  
8 4 **Author**  
9

10 5 Zhenguo Liang<sup>1,2#</sup>, Dongze Wu<sup>3,4#</sup>, Hua Zhang<sup>1#</sup>, Jieruo Gu<sup>2\*</sup>

11 6 Institution

12 7 1.Department of Rheumatology and Immunology, The Fifth Affiliated Hospital of Sun  
13 Yet-Sen University, Zhuhai, Guangdong, China.

14 8 2.Department of Rheumatology, Third Affiliated Hospital of Sun Yat-Sen University,  
15 Guangzhou, Guangdong, China.

16 9 3.Department of Rheumatology and Immunology, Sichuan Provincial People's Hospital,  
17 School of Medicine, University of Electronic Science and Technology of China, Chengdu,  
18 China.

19 10 4.Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital,  
20 Chengdu, China.

21 11 #Contributed equally to this manuscript.

22 12  
23 13  
24 14  
25 15  
26 16  
27 17 **Corresponding authors**

28 18 \*Prof. Jieruo Gu, PhD

29 19 Address: No. 600 Tianhe Road, Tianhe District, Guangzhou, Guangdong, China, 510000

30 20 E-mail: gujieruo@mail.sysu.edu.cn

31 21 Telephone: (+86) 2085253333 / Fax number: (+86) 2085253336

32 22 **Word Count: 3153**      **Table Count: 4**      **Figure Count:1**

33 23 **Conflict of Interest:** The authors confirm that there are no conflicts of interest.

34 24 **Running Head:** Association between asymptomatic hyperuricemia and risk of arthritis.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **25 Abstract**

4  
5 **26 Background**

6  
7 Arthritis is thought to be closely related to serum uric acid. The study aims to assess  
8  
9 the association between asymptomatic hyperuricemia (AH) and arthritis.

10  
11 **29 Methods**

12  
13 A multistage, stratified cluster was used to conduct a cross-sectional study of adult  
14  
15 U.S. civilians aged  $\geq 20$  years from the 2007-2018 National Health and Nutrition  
16  
17 Examination Survey (NHANES). Participants with hyperuricemia and without  
18  
19 hyperuricemia prior to gout were included. A questionnaire was used to determine whether  
20  
21 participants had arthritis and the type of arthritis. Logistic regression was used to  
22  
23 investigate the association between hyperuricemia and arthritis.

24  
25 **36 Result**

26  
27 During the past 12 years, the percentage of participants with arthritis changed from  
28  
29 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA)  
30  
31 increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence  
32  
33 of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30).  
34  
35 Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69),  
36  
37 but the association was muted after adjusting demographic, socioeconomic factors, etc. For  
38  
39 participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI:  
40  
41 1.23, 2.99) and the relationship remained after adjusting for education level, income to  
42  
43 poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00,  
44  
45 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to  
46  
47 develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

48  
49 **48 Conclusion**

50  
51 Our data identified AH as the risk factor for incident arthritis, especially for OA,  
52  
53 which might be exaggerated in aged population and female population.

54  
55  
56  
57  
58  
59  
60 **52 Keywords:** Arthritis, Asymptomatic hyperuricemia, Association, Risk

## 54 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

## 71 Introduction

72 More than one in five adults in the United States had doctor-diagnosed arthritis, and  
73 arthritis-attributable activity limitations significantly increased over time independent of  
74 the population ageing[1]. By 2040, the adults with doctor-diagnosed arthritis are projected  
75 to increase 49% to 78.4 million (1 in 4 US adults), and the arthritis-attributable activity  
76 limitation will increase 52% to 34.6 million (1 in 9 adults)[2]. High medical care  
77 expenditures and earnings losses attributable to arthritis signaling the need for  
78 identification of disease and risk factor that are in most need for interventions[3]. OA as  
79 the most common form of arthritis, involves structural changes in the articular cartilage,  
80 subchondral bones, ligaments, bursae, synovium, and muscles surrounding the joint[4].  
81 From 1990 to 2019, the global age standardized incidence rate of OA increased from 474  
82 to 492 per 100, 000 population and expected to increase due to global population ageing[5,  
83 6]. About 20% of the general population affected by hyperuricemia, which might be more  
84 prominent in male and aged population[7]. Prior research has consistently shown a



1  
2  
3 85 significant correlation between arthritis, particularly OA and rheumatoid arthritis (RA), and  
4  
5 86 hypertension[8]. The intricate relationship between metabolic processes and arthritis,  
6  
7 87 alongside the interplay between metabolic and immunological factors, is garnering  
8  
9 88 heightened attention. Metabolic syndrome's implication in various forms of arthritis, such  
10  
11 89 as OA, is increasingly recognized. [9, 10].

12 90 In 2007-2016, the prevalence of hyperuricemia, gout, and the urate-lowering  
13  
14 91 therapy among patients with gout remained stable[11]. The true significance of  
15  
16 92 asymptomatic hyperuricemia (AH) as a risk factor for incident gout becomes apparent  
17  
18 93 when considering that only half of patients with longstanding hyperuricemia develop  
19  
20 94 clinically evident gout over a 15-year period.[12, 13]. Advanced imaging, including  
21  
22 95 ultrasonography or dual-energy CT, demonstrated approximately 15–40% of patients with  
23  
24 96 chronic hyperuricemia have silent monosodium urate crystal deposition[14]. As the  
25  
26 97 crystallization of monosodium urate marks the progression of hyperuricemia towards gout,  
27  
28 98 it remains uncertain whether hyperuricemia contributes to other forms of arthritis.[15].

29 99 Both hyperuricemia and OA are influenced by common risk factors such as obesity  
30  
31 100 and aging. This shared relationship between risk factors suggests a potential connection  
32  
33 101 between the hyperuricemia and OA, with intraarticular urate contributing to crystallization  
34  
35 102 and cartilage disruption in the context of these shared risk factors.[16]. The predilection for  
36  
37 103 both OA and gout occur in the same joints strongly suggest that OA may predispose to the  
38  
39 104 localized deposition of monosodium urate crystals, which influence structural joint  
40  
41 105 damage[17-19]. Monosodium urate crystals have been shown to inhibit the viability and  
42  
43 106 function of human chondrocytes in vitro with a dose-dependent manner[20]. Death of  
44  
45 107 chondrocytes can lead to an increase in urate, which may even promote crystal deposition  
46  
47 108 on the cartilage, further aggravating OA progression[16]. Monosodium urate crystals  
48  
49 109 inhibit osteocyte viability and, through interactions with macrophages, indirectly promote  
50  
51 110 a shift in osteocyte function that favors bone resorption and inflammation[21]. Uric acid is  
52  
53 111 a danger signal of increasing risk OA through inflammasome activation[22]. Therefore, we  
54  
55 112 hypothesized that hyperuricemia prior to gout was associated with OA. The aim of this  
56  
57 113 study was to i) ascertain the association between AH and arthritis, ii) determine the  
58  
59 114 association between AH and OA, iii) investigate the effect of age and gender on such  
60  
115 association.

## 116 **Patients and methods**

### 117 **Patient and Public Involvement**

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

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

### 137 **Conditions of arthritis**

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

### 145 **Hyperuricemia**

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

1  
2  
3 147 serum uric acid (SUA) at physiological levels is 6.8 mg/dL. This is the saturation point at  
4  
5 148 which urate may precipitate under physiological conditions[25, 26]. We put  $SUA > 6.8$   
6  
7 149 mg/dL was defined as hyperuricemia, and  $SUA \leq 6.8$  mg/dL is defined as the normal state.

## 8 150 **Covariates**

9  
10 151 Covariates are identified in statistical models by means of interview responses and  
11  
12 152 examinations. Covariates that could confound the association between OA and AH were  
13  
14 153 selected based on the results of interviews and examinations in the NHANES database.  
15  
16 154 These factors were chosen to screen for variables that might be associated with OA risk  
17  
18 155 and/or could be associated with AH. This selection aimed to minimize potential  
19  
20 156 confounding variables in the association between OA and AH. The chosen covariates  
21  
22 157 included self-reported demographic characteristics, such as gender, age, race, education  
23  
24 158 level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level  
25  
26 159 (PAL), and diabetes.

27  
28 160 Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race is  
29  
30 161 divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other  
31  
32 162 races. Education is grouped as high school or below, some college and college graduate or  
33  
34 163 above. BMI is calculated from measured weight and height determined by standard  
35  
36 164 NHANES protocols[27]. BMI is categorized as three groups: Normal ( $< 18.5 \text{ kg/m}^2$ ),  
37  
38 165 Overweight ( $18.5\text{--}24.9 \text{ kg/m}^2$ ) and Obesity ( $\geq 25 \text{ kg/m}^2$ ). Participants with systolic blood  
39  
40 166 pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 80$  mmHg are defined as  
41  
42 167 hypertension[28]. PIR as a socioeconomic indicator is stratified into three levels: Low  
43  
44 168 income ( $PIR < 1.3$ ), Middle income ( $1.3 \leq PIR < 3.5$ ) and High income ( $PIR \geq 3.5$ ).

45  
46 169 Smoking status is categorized according to interview results as current (smoked more  
47  
48 170 than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than  
49  
50 171 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100  
51  
52 172 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which  
53  
54 173 includes moderate work activity, walking or cycling, moderate recreational activity, and  
55  
56 174 vigorous activity, which includes vigorous work activity and vigorous recreational activity.  
57  
58 175 Participants with self-reported diabetes had either a diabetes physician's diagnosis of  
59  
60 176 diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance  
177 (OGTT), or/and  $HbA1c \geq 6.5\%$ . Laboratory data included cholesterol, LDL, High-density

1  
2  
3 178 lipoprotein (HDL), triglycerides, creatinine, and albumin.

#### 4 179 **Statistical analysis**

5  
6 180 Design factors involving complex weighting, clustering, and stratification in the  
7  
8 181 NHANES database. Statistical analysis was conducted using STATA (version 16).  
9  
10 182 Complex stratification designs were considered using appropriate sample weights in  
11  
12 183 accordance with NHANES analytical reporting guidelines. In baseline study characteristics,  
13  
14 184 means and standard errors (SEs) were used for continuous variables. Categorical variables  
15  
16 185 were expressed as numbers and percentages. Chi-square test and t-test were used for  
17  
18 186 categorical and continuous variables, respectively. A weighted logistic regression was used  
19  
20 187 to assess the association between OA and AH and to control for confounding factors.  
21  
22 188 Finally, subgroup analysis was performed using hierarchical multivariate regression. The  
23  
24 189 95% confidence intervals and p-values were calculated. A two-tailed test with p-values less  
25  
26 190 than 0.05 are considered significant.

#### 27 191 **Results**

##### 28 192 **The characteristics of study participants**

29 193 A total of 13,647 participants were eligible and included in the analysis from 2007-2008  
30  
31 194 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of  
32  
33 195 participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81%  
34  
35 196 (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09%  
36  
37 197 (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic  
38  
39 198 whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69).  
40  
41 199 Between 2007-2008 and 2017-2018, the proportion of high school or below decreased,  
42  
43 200 which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the  
44  
45 201 proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06,  
46  
47 202 33.00) to 30.47% (95%CI: 24.72, 36.23) (sTable 1).

48 203 During the past 12 years, the percentage of participants with arthritis changed from  
49  
50 204 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from  
51  
52 205 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while  
53  
54 206 the proportion of those who don't know arthritis decreased from 10.13% (95%CI:  
55  
56 207 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis  
57  
58 208 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed

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

211 The 50-59 age group displayed the highest percentage of individuals with AH (19.39%  
212 [95%CI: 17.17, 21.61]) among all the age groups that were examined. A larger proportion  
213 of males (77.17% [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI:  
214 20.63, 25.04]) (Table 1). There are significant differences in race between participants with  
215 and without AH ( $p<0.01$ ). Participants in the AH group had higher levels of obesity,  
216 hypertension, diabetes, LDL, triglycerides, and creatinine than those in the normal state  
217 group (Table 1).

218 The prevalence of patients with OA and AH (11.40% [95%CI: 9.56, 13.24]) is  
219 considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56,  
220 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and unspecified: 7.54% (95%CI: 6.03, 9.05))  
221 ( $p<0.01$ ) (Table 1).

### 222 **The characteristics of hyperuricemia and arthritis**

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

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

Characteristics	Normal state	AH	p value
<b>N*</b>	11387	2260	
<b>Gender</b>			<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)	
<b>Age</b>			<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)	
<b>Race</b>			<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)	
<b>Education Level</b>			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)	
<b>BMI</b>			<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)	
<b>Blood pressure</b>			<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)	
<b>PIR</b>			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)	
	<b>Smoking</b>			<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)	
	<b>PAL</b>			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)	
	<b>Diabetes</b>			<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)	
	<b>Arthritis</b>			<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)	
	<b>Cholesterol(mg/dl) †</b>	191.01±40.22	192.23±41.65	0.1924
	<b>LDL (mg/dl)†</b>	113.39±35.07	115.48±36.82	0.0088
	<b>HDL (mg/dl)†</b>	55.58±15.89	48.87±15.10	<0.01
	<b>Triglycerides(mg/dl) †</b>	110.45±62.12	139.39±73.24	<0.01
	<b>Creatinine(mg/dl)†</b>	122.00±75.58	144.47±82.80	<0.01
	<b>Albumin(mg/dl)†</b>	35.52±320.96	97.29±565.77	<0.01

232 BMI: body mass index; PIR: poverty income ratio; PA: Physical activity level; LDL: Low-density lipoprotein; HDL:  
 233 High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate >  
 234 6.8 mg/dL without gout).  
 235 \*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination  
 236 weight.  
 237 †Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

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

Characteristics	No Arthritis	OA	RA	Other	Unspecified	p value
<b>N*</b>	10089	1402	662	408	1086	
<b>Gender</b>						<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)	
<b>Age</b>						<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)	
<b>Race</b>						<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)	
<b>Education Level</b>						<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)	
<b>BMI</b>						<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)	
<b>Blood pressure</b>						<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)	
<b>PIR</b>						<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)	
<b>Smoking</b>						<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)	
<b>PAL</b>							<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)	
<b>Diabetes</b>							<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)	
<b>Uric acid</b>							<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)	
	<b>Cholesterol(mg/dl) †</b>	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
	<b>LDL (mg/dl) †</b>	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
	<b>HDL (mg/dl) †</b>	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
	<b>Triglycerides(mg/dl) †</b>	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
	<b>Creatinine(mg/dl) †</b>	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
	<b>Albumin(mg/L) †</b>	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01

239 BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL:  
 240 High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate >  
 241 6.8 mg/dL without gout);  
 242 \*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination  
 243 weight.  
 244 †Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

245

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

252 And the proportion of participants who self-reported OA was the highest in arthritis.  
 253 The proportion of AH is higher in participants with OA (84.18% [95%CI: 81.78, 85.59])  
 254 than in those with RA (80.11% [95%CI: 75.97, 84.25]) and unspecified (82.04% [95%CI:  
 255 78.71, 85.36]) arthritis types. But it is slightly lower than no arthritis (84.35% [95%CI:  
 256 83.33, 85.38]) and other arthritis (84.42% [95%CI; 79.68,89.17]) (p<0.01) (Table 2)

### 257 **The association between AH and arthritis**

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

262 **Table 3.** Association between asymptomatic hyperuricemia and total arthritis.

	Unadjusted model	model 1	model 2	model 3
Control (Reference)	1	1	1	1
<b>Total arthritis</b>				
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

263 Model1: Adjusted for age, gender, and race.

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

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

269 For participants aged 40-49 years, AH is significantly associated with incident arthritis  
 270 (OR=1.96, 95%CI: 1.23, 2.99). The association remained after adjusted for education level,  
 271 income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.00, 95%CI:  
 272 1.94, 3.36) (Table 4).

273

274

**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)
<b>Gander</b>			
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
<b>Age</b>			
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
<b>Race</b>			
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

275 Model1: Adjusted for age, gender, and race.

276 Model 2: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, diabetes, hypertension, and  
277 smoking record.278 Model 3: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, hypertension, smoking,  
279 cholesterol, LDL, HDL, triglyceride, creatinine and albumin.

280

281 Among non-Hispanic black participants, AH was significantly associated with arthritis.  
282 (OR=2.02, 95%CI: 1.47, 2.77). The results kept significant adjusting for education level,  
283 income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.31, 95%CI:  
284 1.62, 3.28) and for cholesterol, LDL, HDL, triglyceride, creatinine, and albumin  
285 (OR=2.20,95%CI: 1.55, 3.16) (Table 4).

286 Compared with male participants, female participants with AH showed a higher  
287 likelihood of OA (OR=1.35, 95%CI: 1.14, 1.60). However, for RA (OR: 1.08, 95%CI: 0.83,  
288 1.41), other forms of arthritis (OR: 1.00, 95%CI: 0.78, 1.29), and the 'Unspecified' category  
289 (OR: 0.99, 95%CI: 0.82, 1.20), the observed associations were not statistically significant.

1  
2  
3 290 Notably, this trend was more prominent within the OA subgroup (sTable 2). Among  
4  
5 291 participants aged > 50 years, there is a significant association between AH and different  
6  
7 292 types of arthritis (including OA, RA, other, unspecified). More importantly, the strength of  
8  
9 293 this association increased with age, specifically for 50-59 years, 60-69 years, 70+ years.

## 10 294 **Discussion**

11  
12 295 Based on 12 years of nationally representative data from NHANES, our findings  
13  
14 296 indicated an association between AH and the arthritis, with a notable focus on OA. The  
15  
16 297 correlation was present before adjusting the model. However, after adjusting for additional  
17  
18 298 variables such as cholesterol and creatinine, the correlation weakened, suggesting that the  
19  
20 299 relationship between AH and arthritis (including OA) might not be independent and could  
21  
22 300 be influenced by metabolic and physiological factors like cholesterol and creatinine[29].  
23  
24 301 Our research findings suggest a significant correlation between asymptomatic  
25  
26 302 hyperuricemia (AH) and arthritis among non-Hispanic Black individuals, possibly due to  
27  
28 303 metabolic syndrome-related metabolic abnormalities being less sensitive in identifying  
29  
30 304 elevated uric acid levels in non-Hispanic Black populations [30].

31  
32 305 Although hyperuricemia is a major contributor to the development of gouty arthritis,  
33  
34 306 accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic  
35  
36 307 arthritis and spondylarthritis[31-33]. In vitro studies on synoviocytes from healthy and RA  
37  
38 308 subjects revealed that monosodium urate crystals could increase the release of the  
39  
40 309 inflammatory cytokine IL-6, the chemokine CXCL8 and the matrix metalloproteinase-  
41  
42 310 1[34]. The injection of urate crystals in vivo leads to produce main mediators in the  
43  
44 311 pathogenesis of PsA, such as IL-17 [35]. The hyperuricemia not only play an important  
45  
46 312 role the development and progression of psoriatic arthritis, but also affect severity of  
47  
48 313 clinical manifestations and degree of inflammation[36]. Monosodium urate crystals  
49  
50 314 interact with articular tissues to influence the development of axial spondyloarthritis as  
51  
52 315 monosodium urate crystal deposition associated with the progress of radiographic grade at  
53  
54 316 the sacroiliac joint[18, 37].

55  
56 317 Our data indicate that AH may serve as a marker for potential risk in relation to OA.  
57  
58 318 [22]. An increasing body of evidence suggests that AH, characterized by elevated serum  
59  
60 319 uric acid levels without any symptoms of gout or kidney stone disease, may be associated  
320  
with an increased risk of OA, particularly in weight-bearing joints such as the knee[16, 38,

1  
2  
3 321 39]. The relationship between AH and arthritis is complex and multifaceted, and the exact  
4 322 nature of this relationship is not yet clear. Hyperuricemia may promote the development of  
5 323 arthritis via deposition of urate crystals in the joints, promoting chronic low-grade  
6 324 inflammation, and exacerbating oxidative stress[20, 22, 40]. However, it is also possible  
7 325 that the association between hyperuricemia and arthritis is partially due to common risk  
8 326 factors such as obesity and metabolic syndrome[41, 42]. Further research is needed to  
9 327 better understand the relationship between these two conditions and to identify potential  
10 328 therapeutic targets for the prevention or treatment of arthritis in patients with hyperuricemia.

11 329 The intimate relationship between hyperuricemia and OA may re-purpose FDA-  
12 330 approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used  
13 331 to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs),  
14 332 corticosteroids[43]. However, these drugs could only use to relieve the clinical symptoms  
15 333 but not decrease the onset of arthritis. In accordance with our findings, another study also  
16 334 supports the significant association between arthritis and hypertension[44]. In recent years,  
17 335 there has been growing interest in exploring the role of urate-lowering therapy in the  
18 336 treatment of OA[45]. Urate crystal deposition can directly damage cartilage, stimulate the  
19 337 production of pro-inflammatory cytokines, and lead to inflammation and cartilage  
20 338 degradation[46]. Urate-lowering therapy drugs such as allopurinol and febuxostat have  
21 339 been shown to have anti-inflammatory properties, inhibit the production of reactive oxygen  
22 340 species, reduce the expression of pro-inflammatory cytokine[47-49]. Our results raise the  
23 341 possibility that pharmacological treatment of AH via a treat-to-target (T2T) strategy may  
24 342 decrease incident of arthritis, especially for OA. The T2T strategy involves targeting  
25 343 specific uric acid levels and adjusting drug therapy accordingly to achieve this goal[50,  
26 344 51].

27 345 Our findings highlight those female participants with AH are more likely to develop  
28 346 arthritis, especially for OA, than male participants, and ageing may exaggerate this trend.  
29 347 Among adults in the US, mean uric acid levels were 6.0 mg/dl in men and 4.8 mg/dl in  
30 348 women, and hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[11].  
31 349 Studies have also shown that hyperuricemia is more common in men over 30 and women  
32 350 over 50[52]. The gender and age associated increase in serum uric acid levels may be  
33 351 explained by menopause in women and alcohol consumption in men[53]. Menopause can

1  
2  
3 352 lead to an increase in serum uric acid levels, while postmenopausal hormone replacement  
4 353 therapy may be associated with a decrease in serum uric acid levels[54]. The difference in  
5 354 serum uric acid levels between men and women is due to the increased renal uric acid  
6 355 clearance caused by estrogen in women before menopause[55]. Serum Urate levels were  
7 356 significantly associated with knee OA as determined by osteophytosis in women but not in  
8 357 men[56]. Female typically have a higher prevalence of hand and knee arthritis than males,  
9 358 females also tend to have more severe knee OA, particularly after menopausal age[57].

15 359 The strength of our study was the use of data from a large, nationally representative  
16 360 sample. However, results should be interpreted with caution with inherent limitation. First,  
17 361 it is not possible to interpret the findings from a causal point of view due to the cross-  
18 362 sectional approach. Prospective study and mendelian randomization study are needed to  
19 363 further investigate the relationship between the AH and arthritis, especially OA. Second,  
20 364 recall bias may affect the accuracy of prevalence estimates although this study used CDC-  
21 365 recommended self-reported and physician-diagnosed arthritis as case definitions[24, 58].  
22 366 Third, our result might be charged with choosing a single number to represent prevalent of  
23 367 arthritis in the US population as it only included adults in the national non-institutionalized  
24 368 population of the country[59]. Fourth, medication use for the participants was not included  
25 369 in this study. Finally, we had limited information on the involvement of OA in each  
26 370 participant, such as imaging and treatment procedures.

36 371 In summary, our study results suggest that AH patients may benefit from close  
37 372 monitoring for the development of arthritis, understanding the relationship between  
38 373 hyperuricemia and arthritis, and identifying factors that contribute to their increased risk of  
39 374 these diseases, which may be of great significance for the prevention and management of  
40 375 these conditions.

### 376 **Contributors**

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

### 386 **Funding**

387 Project funded by Guangdong Clinical Research Center of Immune Disease  
388 (2020B1111170008) & Scientific Research Fund of Sichuan Academy of Medical  
389 Sciences (N/A) & Sichuan Provincial People's Hospital (2022QN38).

### 391 **Disclaimer**

392 The funder was not involved in the preparation of this manuscript.

### 394 **Declaration of interests**

395 The authors declare no conflict of interests.

### 397 **Ethical approval**

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

### 403 **Data sharing**

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

## 407 Reference

408

- 409 1. Barbour, K.E., et al., *Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-*  
410 *Attributable Activity Limitation - United States, 2013-2015*. MMWR Morb Mortal Wkly Rep,  
411 2017. **66**(9): p. 246-253.
- 412 2. Hootman, J.M., et al., *Updated Projected Prevalence of Self-Reported Doctor-Diagnosed*  
413 *Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040*. Arthritis  
414 Rheumatol, 2016. **68**(7): p. 1582-7.
- 415 3. Murphy, L.B., et al., *Medical Expenditures and Earnings Losses Among US Adults With*  
416 *Arthritis in 2013*. Arthritis Care Res (Hoboken), 2018. **70**(6): p. 869-876.
- 417 4. Hunter, D.J. and S. Bierma-Zeinstra, *Osteoarthritis*. Lancet, 2019. **393**(10182): p. 1745-  
418 1759.
- 419 5. *Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a*  
420 *systematic analysis for the Global Burden of Disease Study 2019*. Lancet, 2020.  
421 **396**(10258): p. 1204-1222.
- 422 6. Partridge, L., J. Deelen, and P.E. Slagboom, *Facing up to the global challenges of ageing*.  
423 Nature, 2018. **561**(7721): p. 45-56.
- 424 7. Kuo, C.F., et al., *Global epidemiology of gout: prevalence, incidence and risk factors*. Nat  
425 Rev Rheumatol, 2015. **11**(11): p. 649-62.
- 426 8. Liang, X., et al., *Is hypertension associated with arthritis? The United States national health*  
427 *and nutrition examination survey 1999-2018*. Ann Med, 2022. **54**(1): p. 1767-1775.
- 428 9. Bortoluzzi, A., F. Furini, and C.A. Scirè, *Osteoarthritis and its management - Epidemiology,*  
429 *nutritional aspects and environmental factors*. Autoimmun Rev, 2018. **17**(11): p. 1097-1104.
- 430 10. Mobasheri, A., et al., *The role of metabolism in the pathogenesis of osteoarthritis*. Nat Rev  
431 Rheumatol, 2017. **13**(5): p. 302-311.
- 432 11. Chen-Xu, M., et al., *Contemporary Prevalence of Gout and Hyperuricemia in the United*  
433 *States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007-*  
434 *2016*. Arthritis Rheumatol, 2019. **71**(6): p. 991-999.
- 435 12. Dalbeth, N., et al., *Relationship between serum urate concentration and clinically evident*  
436 *incident gout: an individual participant data analysis*. Ann Rheum Dis, 2018. **77**(7): p. 1048-  
437 1052.
- 438 13. Lioté, F. and T. Pascart, *From hyperuricaemia to gout: what are the missing links?* Nat Rev  
439 Rheumatol, 2018. **14**(8): p. 448-449.
- 440 14. Dalbeth, N. and L. Stamp, *Hyperuricaemia and gout: time for a new staging system?* Ann  
441 Rheum Dis, 2014. **73**(9): p. 1598-600.
- 442 15. Dalbeth, N., et al., *Gout*. Lancet, 2021. **397**(10287): p. 1843-1855.



- 1  
2  
3 443 16. Neogi, T., S. Krasnokutsky, and M.H. Pillinger, *Urate and osteoarthritis: Evidence for a*  
4 444 *reciprocal relationship*. Joint Bone Spine, 2019. **86**(5): p. 576-582.
- 5  
6 445 17. Roddy, E., W. Zhang, and M. Doherty, *Are joints affected by gout also affected by*  
7 446 *osteoarthritis?* Ann Rheum Dis, 2007. **66**(10): p. 1374-7.
- 8  
9 447 18. Dalbeth, N., et al., *Relationship between structural joint damage and urate deposition in*  
10 448 *gout: a plain radiography and dual-energy CT study*. Ann Rheum Dis, 2015. **74**(6): p. 1030-  
11 449 6.
- 12  
13 450 19. Yokose, C., et al., *Gout and Osteoarthritis: Associations, Pathophysiology, and*  
14 451 *Therapeutic Implications*. Curr Rheumatol Rep, 2016. **18**(10): p. 65.
- 15  
16 452 20. Chhana, A., et al., *The effects of monosodium urate monohydrate crystals on chondrocyte*  
17 453 *viability and function: implications for development of cartilage damage in gout*. J  
18 454 Rheumatol, 2013. **40**(12): p. 2067-74.
- 19  
20 455 21. Chhana, A., et al., *Monosodium urate crystals reduce osteocyte viability and indirectly*  
21 456 *promote a shift in osteocyte function towards a proinflammatory and proresorptive state*.  
22 457 Arthritis Res Ther, 2018. **20**(1): p. 208.
- 23  
24 458 22. Denoble, A.E., et al., *Uric acid is a danger signal of increasing risk for osteoarthritis through*  
25 459 *inflammasome activation*. Proc Natl Acad Sci U S A, 2011. **108**(5): p. 2088-93.
- 26  
27 460 [dataset] 23. Zhu, Z., et al., *The Association between Retinopathy and Arthritis: Findings from a*  
28 461 *US National Survey 2005-2008*. Curr Eye Res, 2020. **45**(12): p. 1543-1549.
- 29  
30 462 24. March, L.M., et al., *Clinical validation of self-reported osteoarthritis*. Osteoarthritis Cartilage,  
31 463 1998. **6**(2): p. 87-93.
- 32  
33 464 25. Martillo, M.A., L. Nazzari, and D.B. Crittenden, *The crystallization of monosodium urate*.  
34 465 Curr Rheumatol Rep, 2014. **16**(2): p. 400.
- 35  
36 466 26. FitzGerald, J.D., et al., *2020 American College of Rheumatology Guideline for the*  
37 467 *Management of Gout*. Arthritis Care Res (Hoboken), 2020. **72**(6): p. 744-760.
- 38  
39 468 27. *Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-*  
40 469 *94. Series 1: programs and collection procedures*. Vital Health Stat 1, 1994(32): p. 1-407.
- 41  
42 470 28. Whelton, P.K., et al., *2017*  
43 471 *ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the*  
44 472 *Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults:*  
45 473 *Executive Summary: A Report of the American College of Cardiology/American Heart*  
46 474 *Association Task Force on Clinical Practice Guidelines*. Hypertension, 2018. **71**(6): p.  
47 475 1269-1324.
- 48  
49 476 29. Kerekes, G., et al., *Rheumatoid arthritis and metabolic syndrome*. Nat Rev Rheumatol,  
50 477 2014. **10**(11): p. 691-6.
- 51  
52 478 30. DeBoer, M.D. and M.J. Gurka, *Low sensitivity for the metabolic syndrome to detect uric*  
53 479 *acid elevations in females and non-Hispanic-black male adolescents: an analysis of*

- 1  
2  
3  
4 480 *NHANES 1999-2006*. Atherosclerosis, 2012. **220**(2): p. 575-80.
- 5 481 31. Chiou, A., et al., *Coexistent Hyperuricemia and Gout in Rheumatoid Arthritis: Associations*  
6 482 *With Comorbidities, Disease Activity, and Mortality*. Arthritis Care Res (Hoboken), 2020.  
7 483 **72**(7): p. 950-958.
- 8 484 32. Tsuruta, N., S. Imafuku, and Y. Narisawa, *Hyperuricemia is an independent risk factor for*  
9 485 *psoriatic arthritis in psoriatic patients*. J Dermatol, 2017. **44**(12): p. 1349-1352.
- 10 486 33. Ho, H.H., et al., *Coexisting ankylosing spondylitis and gouty arthritis*. Clin Rheumatol, 2007.  
11 487 **26**(10): p. 1655-61.
- 12 488 34. Chen, D.P., et al., *Activation of human fibroblast-like synoviocytes by uric acid crystals in*  
13 489 *rheumatoid arthritis*. Cell Mol Immunol, 2011. **8**(6): p. 469-78.
- 14 490 35. Raucchi, F., et al., *IL-17A neutralizing antibody regulates monosodium urate crystal-induced*  
15 491 *gouty inflammation*. Pharmacol Res, 2019. **147**: p. 104351.
- 16 492 36. Tripolino, C., et al., *Hyperuricemia in Psoriatic Arthritis: Epidemiology, Pathophysiology,*  
17 493 *and Clinical Implications*. Front Med (Lausanne), 2021. **8**: p. 737573.
- 18 494 37. Zhu, J., et al., *Monosodium urate crystal deposition associated with the progress of*  
19 495 *radiographic grade at the sacroiliac joint in axial SpA: a dual-energy CT study*. Arthritis Res  
20 496 Ther, 2017. **19**(1): p. 83.
- 21 497 38. Wang, S., et al., *The association between asymptomatic hyperuricemia and knee*  
22 498 *osteoarthritis: data from the third National Health and Nutrition Examination Survey*.  
23 499 Osteoarthritis Cartilage, 2019. **27**(9): p. 1301-1308.
- 24 500 39. Xiao, L., S. Lin, and F. Zhan, *The association between serum uric acid level and changes*  
25 501 *of MRI findings in knee osteoarthritis: A retrospective study (A STROBE-compliant article)*.  
26 502 Medicine (Baltimore), 2019. **98**(21): p. e15819.
- 27 503 40. Joosten, L.A.B., et al., *Asymptomatic hyperuricaemia: a silent activator of the innate*  
28 504 *immune system*. Nat Rev Rheumatol, 2020. **16**(2): p. 75-86.
- 29 505 41. Zurita-Cruz, J., et al., *Resistin/Uric Acid Index as a Prognostic Factor in Adolescents with*  
30 506 *Obesity after Lifestyle Intervention*. J Pediatr, 2020. **219**: p. 38-42.e1.
- 31 507 42. Musumeci, G., et al., *Osteoarthritis in the XXIst century: risk factors and behaviours that*  
32 508 *influence disease onset and progression*. Int J Mol Sci, 2015. **16**(3): p. 6093-112.
- 33 509 43. Zhang, Y., et al., *Low-dose aspirin use and recurrent gout attacks*. Ann Rheum Dis, 2014.  
34 510 **73**(2): p. 385-90.
- 35 511 44. Krasnokutsky, S., et al., *Serum Urate Levels Predict Joint Space Narrowing in Non-Gout*  
36 512 *Patients With Medial Knee Osteoarthritis*. Arthritis Rheumatol, 2017. **69**(6): p. 1213-1220.
- 37 513 45. Bardin, T. and P. Richette, *Impact of comorbidities on gout and hyperuricaemia: an update*  
38 514 *on prevalence and treatment options*. BMC Med, 2017. **15**(1): p. 123.
- 39 515 46. Schett, G., et al., *Why does the gout attack stop? A roadmap for the immune pathogenesis*  
40 516 *of gout*. RMD Open, 2015. **1**(Suppl 1): p. e000046.

- 1  
2  
3 517 47. Geng, Q., et al., *Febuxostat mitigates IL-18-induced inflammatory response and reduction*  
4 518 *of extracellular matrix gene*. Am J Transl Res, 2021. **13**(3): p. 979-987.
- 5  
6 519 48. Nasi, S., et al., *Xanthine Oxidoreductase Is Involved in Chondrocyte Mineralization and*  
7 520 *Expressed in Osteoarthritic Damaged Cartilage*. Front Cell Dev Biol, 2021. **9**: p. 612440.
- 8  
9 521 49. Li, J., Z. Zhang, and X. Huang, *L-Arginine and allopurinol supplementation attenuates*  
10 522 *inflammatory mediators in human osteoblasts-osteoarthritis cells*. Int J Biol Macromol, 2018.  
11 523 **118**(Pt A): p. 716-721.
- 12  
13 524 50. Kiltz, U., et al., *Treat-to-target (T2T) recommendations for gout*. Ann Rheum Dis, 2017.  
14 525 **76**(4): p. 632-638.
- 15  
16 526 51. Perez-Ruiz, F., et al., *Treat to target in gout*. Rheumatology (Oxford), 2018. **57**(suppl\_1):  
17 527 p. i20-i26.
- 18  
19 528 52. Miao, Z., et al., *Dietary and lifestyle changes associated with high prevalence of*  
20 529 *hyperuricemia and gout in the Shandong coastal cities of Eastern China*. J Rheumatol,  
21 530 2008. **35**(9): p. 1859-64.
- 22  
23 531 53. Lin, K.C., H.Y. Lin, and P. Chou, *The interaction between uric acid level and other risk*  
24 532 *factors on the development of gout among asymptomatic hyperuricemic men in a*  
25 533 *prospective study*. J Rheumatol, 2000. **27**(6): p. 1501-5.
- 26  
27 534 54. Hak, A.E. and H.K. Choi, *Menopause, postmenopausal hormone use and serum uric acid*  
28 535 *levels in US women--the Third National Health and Nutrition Examination Survey*. Arthritis  
29 536 Res Ther, 2008. **10**(5): p. R116.
- 30  
31 537 55. Nicholls, A., M.L. Snaith, and J.T. Scott, *Effect of oestrogen therapy on plasma and urinary*  
32 538 *levels of uric acid*. Br Med J, 1973. **1**(5851): p. 449-51.
- 33  
34 539 56. Ding, X., et al., *The associations of serum uric acid level and hyperuricemia with knee*  
35 540 *osteoarthritis*. Rheumatol Int, 2016. **36**(4): p. 567-73.
- 36  
37 541 57. Srikanth, V.K., et al., *A meta-analysis of sex differences prevalence, incidence and severity*  
38 542 *of osteoarthritis*. Osteoarthritis Cartilage, 2005. **13**(9): p. 769-81.
- 39  
40 543 58. El Miedany, Y., et al., *Incorporating patient reported outcome measures in clinical practice:*  
41 544 *development and validation of a questionnaire for inflammatory arthritis*. Clin Exp  
42 545 Rheumatol, 2010. **28**(5): p. 734-44.
- 43  
44 546 59. Murphy, L.B., et al., *Defining Arthritis for Public Health Surveillance: Methods and*  
45 547 *Estimates in Four US Population Health Surveys*. Arthritis Care Res (Hoboken), 2017.  
46 548 **69**(3): p. 356-367.
- 47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 550 **Figure legends**

4 551 **Figure 1.** Flow chart of sample selection from the NHANES 2007–2018

5  
6 552

7 553 **Supplemental appendix**

8 554 **sTable 1.** Characteristics of participants included in this study.

9 555 **sTable 2.** Subgroup analysis of the association of arthritis subtype (RA, OA, other and  
10  
11 556 unspecified) and AH.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

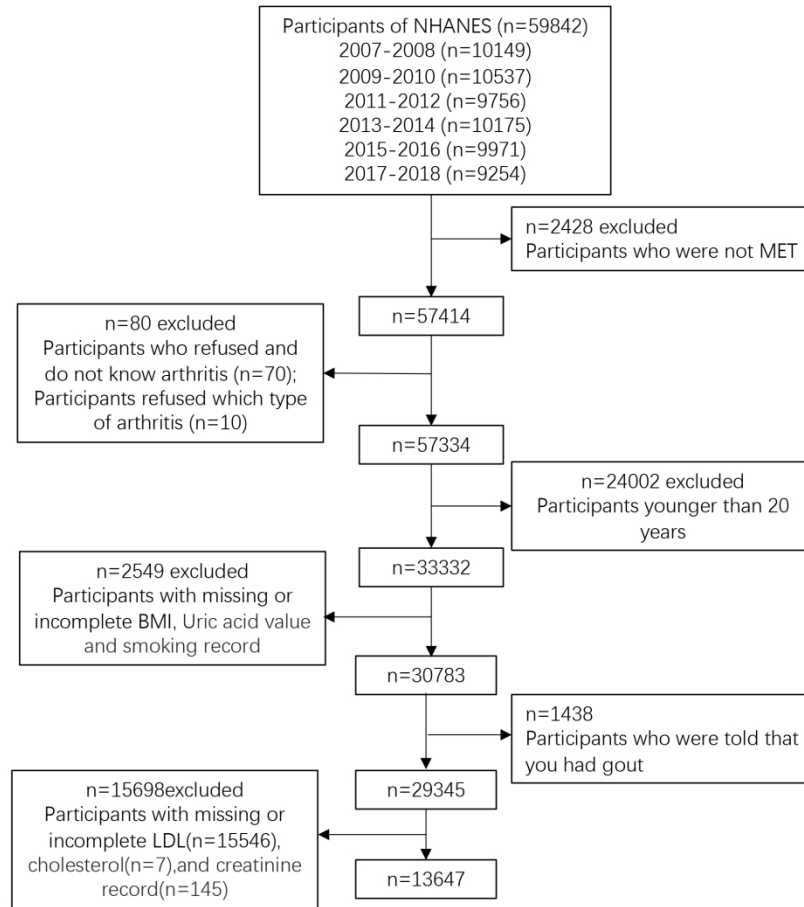


Figure 1. Flow chart of sample selection from the NHANES 2007–2018

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)	

1							
2							
3							
4							
5	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)
6							
7	Education Level						<0.01
8	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)
9	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)
10	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)
11							
12	BMI						<0.01
13							
14	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)
15	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)
16	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)
17							
18	Blood pressure						<0.01
19							
20	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)
21	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)
22							
23	PIR						<0.01
24							
25	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)
26	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)
27	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)
28							
29	Smoking						0.01
30							
31	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)
32	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)
33	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)
34							
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							



1								
2								
3								
4								
5	PAL							<0.01
6								
7	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)	
8	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)	
9								
10	Diabetes							<0.01
11								
12	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)	
13	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)	
14								
15	With or without arthritis							<0.01
16								
17	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)	
18	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)	
19								
20	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)	
21	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)	
22	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)	
23	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)	
24								
25	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
26	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
27	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
28	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
29								
30	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
31	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)
<b>Gander</b>				
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
<b>Age</b>				
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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

1	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	13-14
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5				
6				
7				
8				
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
10				
11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	15
14	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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
20				
21	<b>Other information</b>			
22	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
23				
24				

\*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>.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-074391.R2
Article Type:	Original research
Date Submitted by the Author:	23-Dec-2023
Complete List of Authors:	Liang, Zhenguo; The Fifth Affiliated Hospital of Sun Yat-sen University, Department of Rheumatology and Immunology; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology WU, Dongze; University of Electronic Science and Technology of China Sichuan Provincial People's Hospital, Department of Rheumatology and Immunology Zhang, Hua; The Fifth Affiliated Hospital of Sun Yat-sen University, Department of Rheumatology and Immunology Gu, Jieruo; Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology
<b>Primary Subject Heading</b>:	Immunology (including allergy)
Secondary Subject Heading:	Complementary medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 1 **The association between asymptomatic hyperuricemia and risk of arthritis, findings**  
4 **from a US National Survey 2007-2018**  
5  
6

7 3  
8 4 **Author**  
9

10 5 Zhenguo Liang<sup>1,2#</sup>, Dongze Wu<sup>3#</sup>, Hua Zhang<sup>1#</sup>, Jieruo Gu<sup>2\*</sup>

11 6 Institution

12 7 1.Department of Rheumatology and Immunology, The Fifth Affiliated Hospital of Sun  
13 Yet-Sen University, Zhuhai, Guangdong, China.

14 8 2.Department of Rheumatology, Third Affiliated Hospital of Sun Yat-Sen University,  
15 Guangzhou, Guangdong, China.

16 9 3.Department of Rheumatology and Immunology, Sichuan Provincial People's Hospital,  
17 School of Medicine, University of Electronic Science and Technology of China, Chengdu,  
18 China.

19 10 #Contributed equally to this manuscript.

20 11 **Corresponding authors**

21 12 \*Prof. Jieruo Gu, PhD

22 13 Address: No. 600 Tianhe Road, Tianhe District, Guangzhou, Guangdong, China, 510000

23 14 E-mail: gujieruo@mail.sysu.edu.cn

24 15 Telephone: (+86) 2085253333 / Fax number: (+86) 2085253336

25 16 **Word Count: 3271      Table Count: 4      Figure Count:1**

26 17 **Conflict of Interest:** The authors confirm that there are no conflicts of interest.

27 18 **Running Head:** Association between asymptomatic hyperuricemia and risk of arthritis.  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **23 Abstract**

4  
5 **24 Background**

6  
7 25 Arthritis is thought to be closely related to serum uric acid. The study aims to assess  
8  
9 26 the association between asymptomatic hyperuricemia (AH) and arthritis.

10  
11 **27 Methods**

12  
13 28 A multistage, stratified cluster was used to conduct a cross-sectional study of adult  
14  
15 29 U.S. civilians aged  $\geq 20$  years from the 2007-2018 National Health and Nutrition  
16  
17 30 Examination Survey (NHANES). Participants with hyperuricemia and without  
18  
19 31 hyperuricemia prior to gout were included. A questionnaire was used to determine whether  
20  
21 32 participants had arthritis and the type of arthritis. Logistic regression was used to  
22  
23 33 investigate the association between hyperuricemia and arthritis.

24  
25 **34 Result**

26  
27 35 During the past 12 years, the percentage of participants with arthritis changed from  
28  
29 36 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of osteoarthritis (OA)  
30  
31 37 increased from 8.70% (95%CI: 6.56,10.85) to 12.44% (95%CI: 9.32,15.55), the prevalence  
32  
33 38 of AH changed from 16.35% (95%CI: 14.01,18.40) to 16.39% (95%CI: 13.47,19.30).  
34  
35 39 Participants with AH was associated with onset of arthritis (OR=1.34, 95%CI: 1.07,1.69),  
36  
37 40 but the association was muted after adjusting demographic and socioeconomic factors. For  
38  
39 41 participants aged 40-49 years, AH is associated with incident arthritis (OR=1.96, 95%CI:  
40  
41 42 1.23, 2.99) and the relationship remained after adjusting for education level, income to  
42  
43 43 poverty ratio, body mass index (BMI), diabetes, hypertension, and smoking (OR=2.00,  
44  
45 44 95%CI: 1.94, 3.36). Compared with male, female participants with AH are more likely to  
46  
47 45 develop arthritis, especially in OA (OR=1.35, 95%CI: 1.14, 1.60).

48  
49 **46 Conclusion**

50  
51 47 Our data identified AH as the risk factor for incident arthritis, especially for OA,  
52  
53 48 which might be exaggerated in aged population and female population.

54  
55 49  
56  
57 50 **Keywords:** Arthritis, Asymptomatic hyperuricemia, Association, Risk  
58  
59 51



## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study comprehensively assessed the association between asymptomatic hyperuricemia and arthritis in the United States population aged  $\geq 20$  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].

1  
2  
3 83 In 2007-2016, the prevalence of hyperuricemia, gout, and the urate-lowering  
4  
5 84 therapy among patients with gout remained stable[11]. The true significance of  
6  
7 85 asymptomatic hyperuricemia (AH) as a risk factor for incident gout becomes apparent  
8  
9 86 when considering that only half of patients with longstanding hyperuricemia develop  
10  
11 87 clinically evident gout over a 15-year period.[12, 13]. Advanced imaging, including  
12  
13 88 ultrasonography or dual-energy CT, demonstrated approximately 15–40% of patients with  
14  
15 89 chronic hyperuricemia have silent monosodium urate crystal deposition[14]. As the  
16  
17 90 crystallization of monosodium urate marks the progression of hyperuricemia towards gout,  
18  
19 91 it remains uncertain whether hyperuricemia contributes to other forms of arthritis.[15].

20  
21 92 Both hyperuricemia and OA are influenced by common risk factors such as obesity  
22  
23 93 and aging. This shared relationship between risk factors suggests a potential connection  
24  
25 94 between the hyperuricemia and OA, with intraarticular urate contributing to crystallization  
26  
27 95 and cartilage disruption in the context of these shared risk factors.[16]. The predilection for  
28  
29 96 both OA and gout occur in the same joints strongly suggest that OA may predispose to the  
30  
31 97 localized deposition of monosodium urate crystals, which influence structural joint  
32  
33 98 damage[17-19]. Monosodium urate crystals have been shown to inhibit the viability and  
34  
35 99 function of human chondrocytes in vitro with a dose-dependent manner[20]. Death of  
36  
37 100 chondrocytes can lead to an increase in urate, which may even promote crystal deposition  
38  
39 101 on the cartilage, further aggravating OA progression[16]. Monosodium urate crystals  
40  
41 102 inhibit osteocyte viability and, through interactions with macrophages, indirectly promote  
42  
43 103 a shift in osteocyte function that favors bone resorption and inflammation[21]. Uric acid is  
44  
45 104 a danger signal of increasing risk OA through inflammasome activation[22]. Therefore, we  
46  
47 105 hypothesized that hyperuricemia prior to gout was associated with OA. The aim of this  
48  
49 106 study was to i) ascertain the association between AH and arthritis, ii) determine the  
50  
51 107 association between AH and OA, iii) investigate the effect of age and gender on such  
52  
53 108 association.

## 54 109 **Patients and methods**

### 55 110 **Patient and Public Involvement**

56  
57 111 NHANES is an ongoing longitudinal survey conducted by the National Center for  
58  
59 112 Health Statistics (NCHS) to assess the health and nutritional status of the United States  
60  
113 through a series of interviews and examination items. The NHANES is conducted

1  
2  
3 114 biennially in a nationally representative, non-institutionalized civilian population, and use  
4  
5 115 a hierarchical multi-stage probabilistic clustering design to select a representative sample  
6  
7 116 of over-sampled participants. The sampling methods and examination information used in  
8  
9 117 this study have been described in detail elsewhere[23]. NHANES was reviewed and  
10  
11 118 approved by the NCHS Research Ethics Committee. All manipulations of the NHANES  
12  
13 119 were carried out in accordance with the principles of the Helsinki Declaration. Written  
14  
15 120 informed consent was obtained from all participants in NHANES.

16  
17 121 The study used data from NHANES database for the 2007-2018 study cycle  
18  
19 122 (n=59,842) and excluded those who did not participate in the examination (n=2,428). We  
20  
21 123 excluded participants who refused and don't know ever had or hadn't arthritis, refused to  
22  
23 124 answer which type of arthritis (n=80), who are younger than 20 years old (n=24,002), who  
24  
25 125 have missing and incomplete BMI, uric value, and smoking record (n=2,549). We also  
26  
27 126 excluded participants who were told that you had gout(n=1,438) and participants with  
28  
29 127 missing or incomplete low-density lipoprotein (LDL), cholesterol, and creatinine record.  
30  
31 128 In the end, this study consisted of 13, 647 eligible participants (Figure 1), which is  
32  
33 129 representative of the population size of 87,901,487.

### 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

### 130 **Conditions of arthritis**

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

### 138 **Hyperuricemia**

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

### 143 **Covariates**

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

1  
2  
3 145 examinations. Covariates that could confound the association between OA and AH were  
4 146 selected based on the results of interviews and examinations in the NHANES database.  
5 147 These factors were chosen to screen for variables that might be associated with OA risk  
6 148 and/or could be associated with AH. This selection aimed to minimize potential  
7 149 confounding variables in the association between OA and AH. The chosen covariates  
8 150 included self-reported demographic characteristics, such as gender, age, race, education  
9 151 level, BMI, blood pressure, poverty income ratio (PIR), smoking, physical activity level  
10 152 (PAL), and diabetes.

11 153 Age is divided into seven groups: 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. Race is  
12 154 divided into four groups: non-Hispanic white, non-Hispanic black, Hispanic and other  
13 155 races. Education is grouped as high school or below, some college and college graduate or  
14 156 above. BMI is calculated from measured weight and height determined by standard  
15 157 NHANES protocols[27]. BMI is categorized as three groups: Normal ( $<18.5\text{kg/m}^2$ ),  
16 158 Overweight ( $18.5\text{--}24.9\text{kg/m}^2$ ) and Obesity ( $\geq 25\text{kg/m}^2$ ). Participants with systolic blood  
17 159 pressure  $\geq 130\text{ mmHg}$  or diastolic blood pressure  $\geq 80\text{ mmHg}$  are defined as  
18 160 hypertension[28]. PIR as a socioeconomic indicator is stratified into three levels: Low  
19 161 income ( $\text{PIR} < 1.3$ ), Middle income ( $1.3 \leq \text{PIR} < 3.5$ ) and High income ( $\text{PIR} \geq 3.5$ ).

20 162 Smoking status is categorized according to interview results as current (smoked more  
21 163 than 100 cigarettes in the lifetime and currently still smoked), before (smoked more than  
22 164 100 cigarettes in the lifetime but did not currently smoke) and never (smoked less than 100  
23 165 cigarettes in the lifetime). PAL is divided into two categories, moderate activity, which  
24 166 includes moderate work activity, walking or cycling, moderate recreational activity, and  
25 167 vigorous activity, which includes vigorous work activity and vigorous recreational activity.  
26 168 Participants with self-reported diabetes had either a diabetes physician's diagnosis of  
27 169 diabetes or an elevated fasting plasma glucose level or an elevated oral glucose tolerance  
28 170 (OGTT), or/and  $\text{HbA1c} \geq 6.5\%$ . Laboratory data included cholesterol, LDL, High-density  
29 171 lipoprotein (HDL), triglycerides, creatinine, and albumin.

## 30 172 **Statistical analysis**

31 173 Design factors involving complex weighting, clustering, and stratification in the  
32 174 NHANES database. Statistical analysis was conducted using STATA (version 16).  
33 175 Complex stratification designs were considered using appropriate sample weights in

1  
2  
3 176 accordance with NHANES analytical reporting guidelines. In baseline study characteristics,  
4 177 means and standard errors (SEs) were used for continuous variables. Categorical variables  
5 178 were expressed as numbers and percentages. Chi-square test and t-test were used for  
6  
7 179 categorical and continuous variables, respectively. A weighted logistic regression was used  
8  
9 180 to assess the association between OA and AH and to control for confounding factors.  
10  
11 181 Finally, subgroup analysis was performed using hierarchical multivariate regression. The  
12  
13 182 95% confidence intervals and p-values were calculated. A two-tailed test with p-values less  
14  
15 183 than 0.05 are considered significant.

## 17 184 **Results**

### 18 185 **The characteristics of study participants**

19 186 A total of 13,647 participants were eligible and included in the analysis from 2007-2008  
20 187 to 2017-2018 (sTable 1). Between 2007-2008 and 2017-2018, the proportion of  
21 188 participants in the 60-69 age group increased from 11.44% (95%CI: 9.42, 13.46) to 14.81%  
22 189 (95%CI: 11.45, 18.16). In addition, the proportion of Hispanics increased from 5.09%  
23 190 (95%CI: 2.60, 7.58) to 6.86% (95%CI: 5.00, 8.72), while the proportion of non-Hispanic  
24 191 whites decreased from 70.37% (95%CI: 63.63, 77.11) to 61.96% (95%CI: 57.22, 66.69).  
25 192 Between 2007-2008 and 2017-2018, the proportion of high school or below decreased,  
26 193 which is from 43.02% (95%CI: 37.88, 48.16) to 39.61% (95%CI: 36.03, 43.19), while the  
27 194 proportion of college graduate or above increased, which was from 28.53% (95%CI: 24.06,  
28 195 33.00) to 30.47% (95%CI: 24.72, 36.23) (sTable 1).

29 196 During the past 12 years, the percentage of participants with arthritis changed from  
30 197 25.95% (22.53, 29.36) to 25.53% (21.62, 29.44). The prevalence of RA increased from  
31 198 3.57% (95%CI: 2.87,4.27) in 2007-2008 to 4.04% (95%CI: 2.82,5.25) in 2017-2018, while  
32 199 the proportion of those who don't know arthritis decreased from 10.13% (95%CI:  
33 200 8.22,12.05) to 6.02% (95%CI: 4.66,7.37). There was also a little decrease in other arthritis  
34 201 3.54% (95%CI: 2.56,4.52) and 3.04% (95%CI: 1.78,4.30). The prevalence of OA showed  
35 202 a clear upward trend during the 12 years, from 8.70% (95%CI: 6.56, 10.85) in 2007-2008  
36 203 to 12.44% (95%CI: 9.32, 15.55) in 2017-2018 (p<0.01) (sTable 1).

37 204 The 50-59 age group displayed the highest percentage of individuals with AH (19.39%  
38 205 [95%CI: 17.17, 21.61]) among all the age groups that were examined. A larger proportion  
39 206 of males (77.17% [95%CI: 74.96, 79.37]) had AH compared with females (22.83 [95%CI:

1  
2  
3 207 20.63, 25.04]) (Table 1). There are significant differences in race between participants with  
4  
5 208 and without AH ( $p < 0.01$ ). Participants in the AH group had higher levels of obesity,  
6  
7 209 hypertension, diabetes, LDL, triglycerides, and creatinine than those in the normal state  
8  
9 210 group (Table 1).

10 211 The prevalence of patients with OA and AH (11.40% [95%CI: 9.56, 13.24]) is  
11  
12 212 considerably higher than that of other three types of arthritis (RA: 4.62% (95%CI: 3.56,  
13  
14 213 5.69), Other: 3.14% (95%CI: 2.12, 4.17) and unspecified: 7.54% (95%CI: 6.03, 9.05))  
15  
16 214 ( $p < 0.01$ ) (Table 1).

### 17 215 **The characteristics of hyperuricemia and arthritis**

18  
19 216 The higher frequency of participants with arthritis, including OA, RA, other forms, and  
20  
21 217 those who were unaware of having arthritis, among individuals aged over 50 years,  
22  
23 218 suggests that age may be a contributing factor to the prevalence of arthritis in this  
24  
25 219 population (Table 2). The characteristics of the 13,647 participants included in our study  
26  
27 220 with self-reported OA, RA, other, and Unspecified are presented using weighted statistics  
28  
29 221 (Table 1). The prevalence of the four types of arthritis was higher among female  
30  
31 222 participants than among male participants, which was most notable in OA (female: 65.94%  
32  
33 223 vs male 34.06%) (Table 2).  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

Characteristics	Normal state	AH	p value
<b>N*</b>	11387	2260	
<b>Gender</b>			<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)	
<b>Age</b>			<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)	
<b>Race</b>			<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)	
<b>Education Level</b>			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)	
<b>BMI</b>			<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)	
<b>Blood pressure</b>			<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)	
<b>PIR</b>			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)	
	<b>Smoking</b>			<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)	
	<b>PAL</b>			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)	
	<b>Diabetes</b>			<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)	
	<b>Arthritis</b>			<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)	
	<b>Cholesterol(mg/dl) †</b>	191.01±40.22	192.23±41.65	0.1924
	<b>LDL (mg/dl)†</b>	113.39±35.07	115.48±36.82	0.0088
	<b>HDL (mg/dl)†</b>	55.58±15.89	48.87±15.10	<0.01
	<b>Triglycerides(mg/dl) †</b>	110.45±62.12	139.39±73.24	<0.01
	<b>Creatinine(mg/dl)†</b>	122.00±75.58	144.47±82.80	<0.01
	<b>Albumin(mg/dl)†</b>	35.52±320.96	97.29±565.77	<0.01

225 BMI: body mass index; PIR: poverty income ratio; PA: Physical activity level; LDL: Low-density lipoprotein; HDL:  
 226 High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate >  
 227 6.8 mg/dL without gout).

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

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



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

Characteristics	No Arthritis	OA	RA	Other	Unspecified	p value
<b>N*</b>	10089	1402	662	408	1086	
<b>Gender</b>						<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)	
<b>Age</b>						<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)	
<b>Race</b>						<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)	
<b>Education Level</b>						<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)	
<b>BMI</b>						<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)	
<b>Blood pressure</b>						<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)	
<b>PIR</b>						<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)	
<b>Smoking</b>						<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)	
<b>PAL</b>							<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)	
<b>Diabetes</b>							<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)	
<b>Uric acid</b>							<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)	
	<b>Cholesterol(mg/dl) †</b>	190.59±40.19	194.85±42.44	190.37±39.50	192.29±39.04	192.42±41.20	0.0041
	<b>LDL (mg/dl) †</b>	113.95±35.17	113.39±36.73	111.54±35.07	112.34±34.79	113.58±35.80	0.256
	<b>HDL (mg/dl) †</b>	54.09±15.69	57.40±17.82	54.48±15.65	54.68±16.01	54.09±15.71	<0.01
	<b>Triglycerides(mg/dl) †</b>	112.74±65.21	120.35±63.20	121.79±63.47	126.30±70.36	123.75±62.26	0.015
	<b>Creatinine(mg/dl) †</b>	129.07±79.51	111.90±67.15	118.38±72.13	122.80±68.54	118.03±71.54	<0.01
	<b>Albumin(mg/L) †</b>	38.98±354.61	54.86±421.95	67.42±349.01	46.01±258.35	83.60±558.69	<0.01

232 BMI: body mass index; PIR: poverty income ratio; PAL: Physical activity level; LDL: Low-density lipoprotein; HDL:  
 233 High-density lipoprotein; RA: Rheumatoid arthritis; OA: Osteoarthritis; AH: asymptomatic hyperuricemia (serum urate >  
 234 6.8 mg/dL without gout);  
 235 \*N represents unweighted number, and the remaining values are weighted values using NHANES MEC examination  
 236 weight.  
 237 †Figures are expressed as mean ± standard error, other figures are expressed as percent (95% confidence intervals).

238

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

245 And the proportion of participants who self-reported OA was the highest in arthritis.  
 246 The proportion of AH is higher in participants with OA (84.18% [95%CI: 81.78, 85.59])  
 247 than in those with RA (80.11% [95%CI: 75.97, 84.25]) and unspecified (82.04% [95%CI:  
 248 78.71, 85.36]) arthritis types. But it is slightly lower than no arthritis (84.35% [95%CI:  
 249 83.33, 85.38]) and other arthritis (84.42% [95%CI; 79.68,89.17]) (p<0.01) (Table 2)

### 250 **The association between AH and arthritis**

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

255 **Table 3.** Association between asymptomatic hyperuricemia and total arthritis.

	Unadjusted model	model 1	model 2	model 3
Control (Reference)	1	1	1	1
<b>Total arthritis</b>				
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

256 Model1: Adjusted for age, gender, and race.

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

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

262 For participants aged 40-49 years, AH is significantly associated with incident arthritis  
 263 (OR=1.96, 95%CI: 1.23, 2.99). The association remained after adjusted for education level,  
 264 income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.00, 95%CI:  
 265 1.94, 3.36) (Table 4).

266

267 **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)
<b>Gander</b>			
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
<b>Age</b>			
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
<b>Race</b>			
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

268 Model1: Adjusted for age, gender, and race.

269 Model 2: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, diabetes, hypertension, and  
270 smoking record.271 Model 3: Adjusted for age, gender, race, education level, income to poverty ratio, BMI, hypertension, smoking,  
272 cholesterol, LDL, HDL, triglyceride, creatinine and albumin.

273

274 Among non-Hispanic black participants, AH was significantly associated with arthritis.  
275 (OR=2.02, 95%CI: 1.47, 2.77). The results kept significant adjusting for education level,  
276 income to poverty ratio, BMI, diabetes, hypertension, and smoking (OR=2.31, 95%CI:  
277 1.62, 3.28) and for cholesterol, LDL, HDL, triglyceride, creatinine, and albumin  
278 (OR=2.20,95%CI: 1.55, 3.16) (Table 4).

279 Compared with male participants, female participants with AH showed a higher  
280 likelihood of OA (OR=1.35, 95%CI: 1.14, 1.60). However, for RA (OR: 1.08, 95%CI: 0.83,  
281 1.41), other forms of arthritis (OR: 1.00, 95%CI: 0.78, 1.29), and the 'Unspecified' category  
282 (OR: 0.99, 95%CI: 0.82, 1.20), the observed associations were not statistically significant.

1  
2  
3 283 Notably, this trend was more prominent within the OA subgroup (sTable 2). Among  
4 284 participants aged > 50 years, there is a significant association between AH and different  
5 285 types of arthritis (including OA, RA, other, unspecified). More importantly, the strength of  
6 286 this association increased with age, specifically for 50-59 years, 60-69 years, 70+ years.

## 10 287 **Discussion**

11 288 Based on 12 years of nationally representative data from NHANES, our findings  
12 289 indicated an association between AH and the arthritis, with a notable focus on OA. The  
13 290 correlation was present before adjusting the model. However, after adjusting for additional  
14 291 variables such as cholesterol and creatinine, the correlation weakened, suggesting that the  
15 292 relationship between AH and arthritis (including OA) might not be independent and could  
16 293 be influenced by metabolic and physiological factors like cholesterol and creatinine[29].  
17 294 Our research findings suggest a significant correlation between asymptomatic  
18 295 hyperuricemia (AH) and arthritis among non-Hispanic Black individuals, possibly due to  
19 296 metabolic syndrome-related metabolic abnormalities being less sensitive in identifying  
20 297 elevated uric acid levels in non-Hispanic Black populations [30].

21 298 Although hyperuricemia is a major contributor to the development of gouty arthritis,  
22 299 accumulating evidence suggest that AH may increase the risk of developing RA, psoriatic  
23 300 arthritis and spondylarthritis[31-33]. In vitro studies on synoviocytes from healthy and RA  
24 301 subjects revealed that monosodium urate crystals could increase the release of the  
25 302 inflammatory cytokine IL-6, the chemokine CXCL8 and the matrix metalloproteinase-  
26 303 1[34]. The injection of urate crystals in vivo leads to produce main mediators in the  
27 304 pathogenesis of PsA, such as IL-17 [35]. The hyperuricemia not only play an important  
28 305 role the development and progression of psoriatic arthritis, but also affect severity of  
29 306 clinical manifestations and degree of inflammation[36]. Monosodium urate crystals  
30 307 interact with articular tissues to influence the development of axial spondyloarthritis as  
31 308 monosodium urate crystal deposition associated with the progress of radiographic grade at  
32 309 the sacroiliac joint[18, 37].

33 310 Our data indicate that AH may serve as a marker for potential risk in relation to OA.  
34 311 [22]. An increasing body of evidence suggests that AH, characterized by elevated serum  
35 312 uric acid levels without any symptoms of gout or kidney stone disease, may be associated  
36 313 with an increased risk of OA, particularly in weight-bearing joints such as the knee[16, 38,

1  
2  
3 314 39]. The relationship between AH and arthritis is complex and multifaceted, and the exact  
4 315 nature of this relationship is not yet clear. Hyperuricemia may promote the development of  
5 316 arthritis via deposition of urate crystals in the joints, promoting chronic low-grade  
6 317 inflammation, and exacerbating oxidative stress[20, 22, 40]. However, it is also possible  
7 318 that the association between hyperuricemia and arthritis is partially due to common risk  
8 319 factors such as obesity and metabolic syndrome[41, 42]. Further research is needed to  
9 320 better understand the relationship between these two conditions and to identify potential  
10 321 therapeutic targets for the prevention or treatment of arthritis in patients with hyperuricemia.

11 322 The intimate relationship between hyperuricemia and OA may re-purpose FDA-  
12 323 approved urate-lowering therapy drugs in the treatment of OA. Currently, the drugs used  
13 324 to treat OA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs),  
14 325 corticosteroids[43]. However, these drugs could only use to relieve the clinical symptoms  
15 326 but not decrease the onset of arthritis. In accordance with our findings, another study also  
16 327 supports the significant association between arthritis and hypertension[44]. In recent years,  
17 328 there has been growing interest in exploring the role of urate-lowering therapy in the  
18 329 treatment of OA[45]. Urate crystal deposition can directly damage cartilage, stimulate the  
19 330 production of pro-inflammatory cytokines, and lead to inflammation and cartilage  
20 331 degradation[46]. Urate-lowering therapy drugs such as allopurinol and febuxostat have  
21 332 been shown to have anti-inflammatory properties, inhibit the production of reactive oxygen  
22 333 species, reduce the expression of pro-inflammatory cytokine[47-49]. Our results raise the  
23 334 possibility that pharmacological treatment of AH via a treat-to-target (T2T) strategy may  
24 335 decrease incident of arthritis, especially for OA. The T2T strategy involves targeting  
25 336 specific uric acid levels and adjusting drug therapy accordingly to achieve this goal[50,  
26 337 51].

27 338 Our findings highlight those female participants with AH are more likely to develop  
28 339 arthritis, especially for OA, than male participants, and ageing may exaggerate this trend.  
29 340 Among adults in the US, serum urate was 6.0 mg/dl in men and 4.8 mg/dl in women, and  
30 341 hyperuricemia prevalence rates were 20.2% and 20.0%, respectively[11]. Studies have also  
31 342 shown that hyperuricemia is more common in men over 30 and women over 50[52]. The  
32 343 gender and age associated increase in serum uric acid levels may be explained by  
33 344 menopause in women and alcohol consumption in men[53]. Menopause can lead to an

1  
2  
3 345 increase in serum uric acid levels, while postmenopausal hormone replacement therapy  
4 346 may be associated with a decrease in serum uric acid levels[54]. The difference in serum  
5 347 uric acid levels between men and women is due to the increased renal uric acid clearance  
6 348 caused by estrogen in women before menopause[55]. Serum Urate levels were significantly  
7 349 associated with knee OA as determined by osteophytosis in women but not in men[56].  
8 350 Female typically have a higher prevalence of hand and knee arthritis than males, females  
9 351 also tend to have more severe knee OA, particularly after menopausal age[57].

15 352 The strength of our study was the use of data from a large, nationally representative  
16 353 sample. However, results should be interpreted with caution with inherent limitation. First,  
17 354 it is not possible to interpret the findings from a causal point of view due to the cross-  
18 355 sectional approach. Prospective study and mendelian randomization study are needed to  
19 356 further investigate the relationship between the AH and arthritis, especially OA. Second,  
20 357 recall bias may affect the accuracy of prevalence estimates although this study used CDC-  
21 358 recommended self-reported and physician-diagnosed arthritis as case definitions[24, 58].  
22 359 Third, our result might be charged with choosing a single number to represent prevalent of  
23 360 arthritis in the US population as it only included adults in the national non-institutionalized  
24 361 population of the country[59]. Fourth, medication use for the participants was not included  
25 362 in this study. Finally, we had limited information on the involvement of OA in each  
26 363 participant, such as imaging and treatment procedures.

36 364 In summary, our study results suggest that AH patients may benefit from close  
37 365 monitoring for the development of arthritis, understanding the relationship between  
38 366 hyperuricemia and arthritis, and identifying factors that contribute to their increased risk of  
39 367 these diseases, which may be of great significance for the prevention and management of  
40 368 these conditions.

### 369 **Contributors**

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

378

### 379 **Funding**

380 Project funded by Guangdong Clinical Research Center of Immune Disease  
381 (2020B1111170008) & Scientific Research Fund of Sichuan Academy of Medical  
382 Sciences (N/A) & Sichuan Provincial People's Hospital (2022QN38).

383

### 384 **Disclaimer**

385 The funder was not involved in the preparation of this manuscript.

386

### 387 **Declaration of interests**

388 The authors declare no conflict of interests.

389

### 390 **Ethical approval**

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

395

### 396 **Data sharing**

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

400



## 400 Reference

401

- 402 1. Barbour, K.E., et al., *Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-*  
403 *Attributable Activity Limitation - United States, 2013-2015*. MMWR Morb Mortal Wkly Rep,  
404 2017. **66**(9): p. 246-253.
- 405 2. Hootman, J.M., et al., *Updated Projected Prevalence of Self-Reported Doctor-Diagnosed*  
406 *Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040*. Arthritis  
407 Rheumatol, 2016. **68**(7): p. 1582-7.
- 408 3. Murphy, L.B., et al., *Medical Expenditures and Earnings Losses Among US Adults With*  
409 *Arthritis in 2013*. Arthritis Care Res (Hoboken), 2018. **70**(6): p. 869-876.
- 410 4. Hunter, D.J. and S. Bierma-Zeinstra, *Osteoarthritis*. Lancet, 2019. **393**(10182): p. 1745-  
411 1759.
- 412 5. *Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a*  
413 *systematic analysis for the Global Burden of Disease Study 2019*. Lancet, 2020.  
414 **396**(10258): p. 1204-1222.
- 415 6. Partridge, L., J. Deelen, and P.E. Slagboom, *Facing up to the global challenges of ageing*.  
416 Nature, 2018. **561**(7721): p. 45-56.
- 417 7. Kuo, C.F., et al., *Global epidemiology of gout: prevalence, incidence and risk factors*. Nat  
418 Rev Rheumatol, 2015. **11**(11): p. 649-62.
- 419 8. Liang, X., et al., *Is hypertension associated with arthritis? The United States national health*  
420 *and nutrition examination survey 1999-2018*. Ann Med, 2022. **54**(1): p. 1767-1775.
- 421 9. Bortoluzzi, A., F. Furini, and C.A. Scirè, *Osteoarthritis and its management - Epidemiology,*  
422 *nutritional aspects and environmental factors*. Autoimmun Rev, 2018. **17**(11): p. 1097-1104.
- 423 10. Mobasheri, A., et al., *The role of metabolism in the pathogenesis of osteoarthritis*. Nat Rev  
424 Rheumatol, 2017. **13**(5): p. 302-311.
- 425 11. Chen-Xu, M., et al., *Contemporary Prevalence of Gout and Hyperuricemia in the United*  
426 *States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007-*  
427 *2016*. Arthritis Rheumatol, 2019. **71**(6): p. 991-999.
- 428 12. Dalbeth, N., et al., *Relationship between serum urate concentration and clinically evident*  
429 *incident gout: an individual participant data analysis*. Ann Rheum Dis, 2018. **77**(7): p. 1048-  
430 1052.
- 431 13. Lioté, F. and T. Pascart, *From hyperuricaemia to gout: what are the missing links?* Nat Rev  
432 Rheumatol, 2018. **14**(8): p. 448-449.
- 433 14. Dalbeth, N. and L. Stamp, *Hyperuricaemia and gout: time for a new staging system?* Ann  
434 Rheum Dis, 2014. **73**(9): p. 1598-600.
- 435 15. Dalbeth, N., et al., *Gout*. Lancet, 2021. **397**(10287): p. 1843-1855.

- 1  
2  
3 436 16. Neogi, T., S. Krasnokutsky, and M.H. Pillinger, *Urate and osteoarthritis: Evidence for a*  
4 437 *reciprocal relationship*. Joint Bone Spine, 2019. **86**(5): p. 576-582.
- 5  
6 438 17. Roddy, E., W. Zhang, and M. Doherty, *Are joints affected by gout also affected by*  
7 439 *osteoarthritis?* Ann Rheum Dis, 2007. **66**(10): p. 1374-7.
- 8  
9 440 18. Dalbeth, N., et al., *Relationship between structural joint damage and urate deposition in*  
10 441 *gout: a plain radiography and dual-energy CT study*. Ann Rheum Dis, 2015. **74**(6): p. 1030-  
11 442 6.
- 12  
13 443 19. Yokose, C., et al., *Gout and Osteoarthritis: Associations, Pathophysiology, and*  
14 444 *Therapeutic Implications*. Curr Rheumatol Rep, 2016. **18**(10): p. 65.
- 15  
16 445 20. Chhana, A., et al., *The effects of monosodium urate monohydrate crystals on chondrocyte*  
17 446 *viability and function: implications for development of cartilage damage in gout*. J  
18 447 Rheumatol, 2013. **40**(12): p. 2067-74.
- 19  
20 448 21. Chhana, A., et al., *Monosodium urate crystals reduce osteocyte viability and indirectly*  
21 449 *promote a shift in osteocyte function towards a proinflammatory and proresorptive state*.  
22 450 Arthritis Res Ther, 2018. **20**(1): p. 208.
- 23  
24 451 22. Denoble, A.E., et al., *Uric acid is a danger signal of increasing risk for osteoarthritis through*  
25 452 *inflammasome activation*. Proc Natl Acad Sci U S A, 2011. **108**(5): p. 2088-93.
- 26  
27 453 [dataset] 23. Zhu, Z., et al., *The Association between Retinopathy and Arthritis: Findings from a*  
28 454 *US National Survey 2005-2008*. Curr Eye Res, 2020. **45**(12): p. 1543-1549.
- 29  
30 455 24. March, L.M., et al., *Clinical validation of self-reported osteoarthritis*. Osteoarthritis Cartilage,  
31 456 1998. **6**(2): p. 87-93.
- 32  
33 457 25. Martillo, M.A., L. Nazzari, and D.B. Crittenden, *The crystallization of monosodium urate*.  
34 458 Curr Rheumatol Rep, 2014. **16**(2): p. 400.
- 35  
36 459 26. FitzGerald, J.D., et al., *2020 American College of Rheumatology Guideline for the*  
37 460 *Management of Gout*. Arthritis Care Res (Hoboken), 2020. **72**(6): p. 744-760.
- 38  
39 461 27. *Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-*  
40 462 *94. Series 1: programs and collection procedures*. Vital Health Stat 1, 1994(32): p. 1-407.
- 41  
42 463 28. Whelton, P.K., et al., *2017*  
43 464 *ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the*  
44 465 *Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults:*  
45 466 *Executive Summary: A Report of the American College of Cardiology/American Heart*  
46 467 *Association Task Force on Clinical Practice Guidelines*. Hypertension, 2018. **71**(6): p.  
47 468 1269-1324.
- 48  
49 469 29. Kerekes, G., et al., *Rheumatoid arthritis and metabolic syndrome*. Nat Rev Rheumatol,  
50 470 2014. **10**(11): p. 691-6.
- 51  
52 471 30. DeBoer, M.D. and M.J. Gurka, *Low sensitivity for the metabolic syndrome to detect uric*  
53 472 *acid elevations in females and non-Hispanic-black male adolescents: an analysis of*

- 1  
2  
3  
4 473 *NHANES 1999-2006. Atherosclerosis*, 2012. **220**(2): p. 575-80.
- 5 474 31. Chiou, A., et al., *Coexistent Hyperuricemia and Gout in Rheumatoid Arthritis: Associations*  
6 475 *With Comorbidities, Disease Activity, and Mortality*. *Arthritis Care Res (Hoboken)*, 2020.  
7 476 **72**(7): p. 950-958.
- 8 477 32. Tsuruta, N., S. Imafuku, and Y. Narisawa, *Hyperuricemia is an independent risk factor for*  
9 478 *psoriatic arthritis in psoriatic patients*. *J Dermatol*, 2017. **44**(12): p. 1349-1352.
- 10 479 33. Ho, H.H., et al., *Coexisting ankylosing spondylitis and gouty arthritis*. *Clin Rheumatol*, 2007.  
11 480 **26**(10): p. 1655-61.
- 12 481 34. Chen, D.P., et al., *Activation of human fibroblast-like synoviocytes by uric acid crystals in*  
13 482 *rheumatoid arthritis*. *Cell Mol Immunol*, 2011. **8**(6): p. 469-78.
- 14 483 35. Raucchi, F., et al., *IL-17A neutralizing antibody regulates monosodium urate crystal-induced*  
15 484 *gouty inflammation*. *Pharmacol Res*, 2019. **147**: p. 104351.
- 16 485 36. Tripolino, C., et al., *Hyperuricemia in Psoriatic Arthritis: Epidemiology, Pathophysiology,*  
17 486 *and Clinical Implications*. *Front Med (Lausanne)*, 2021. **8**: p. 737573.
- 18 487 37. Zhu, J., et al., *Monosodium urate crystal deposition associated with the progress of*  
19 488 *radiographic grade at the sacroiliac joint in axial SpA: a dual-energy CT study*. *Arthritis Res*  
20 489 *Ther*, 2017. **19**(1): p. 83.
- 21 490 38. Wang, S., et al., *The association between asymptomatic hyperuricemia and knee*  
22 491 *osteoarthritis: data from the third National Health and Nutrition Examination Survey*.  
23 492 *Osteoarthritis Cartilage*, 2019. **27**(9): p. 1301-1308.
- 24 493 39. Xiao, L., S. Lin, and F. Zhan, *The association between serum uric acid level and changes*  
25 494 *of MRI findings in knee osteoarthritis: A retrospective study (A STROBE-compliant article)*.  
26 495 *Medicine (Baltimore)*, 2019. **98**(21): p. e15819.
- 27 496 40. Joosten, L.A.B., et al., *Asymptomatic hyperuricaemia: a silent activator of the innate*  
28 497 *immune system*. *Nat Rev Rheumatol*, 2020. **16**(2): p. 75-86.
- 29 498 41. Zurita-Cruz, J., et al., *Resistin/Uric Acid Index as a Prognostic Factor in Adolescents with*  
30 499 *Obesity after Lifestyle Intervention*. *J Pediatr*, 2020. **219**: p. 38-42.e1.
- 31 500 42. Musumeci, G., et al., *Osteoarthritis in the XXIst century: risk factors and behaviours that*  
32 501 *influence disease onset and progression*. *Int J Mol Sci*, 2015. **16**(3): p. 6093-112.
- 33 502 43. Zhang, Y., et al., *Low-dose aspirin use and recurrent gout attacks*. *Ann Rheum Dis*, 2014.  
34 503 **73**(2): p. 385-90.
- 35 504 44. Krasnokutsky, S., et al., *Serum Urate Levels Predict Joint Space Narrowing in Non-Gout*  
36 505 *Patients With Medial Knee Osteoarthritis*. *Arthritis Rheumatol*, 2017. **69**(6): p. 1213-1220.
- 37 506 45. Bardin, T. and P. Richette, *Impact of comorbidities on gout and hyperuricaemia: an update*  
38 507 *on prevalence and treatment options*. *BMC Med*, 2017. **15**(1): p. 123.
- 39 508 46. Schett, G., et al., *Why does the gout attack stop? A roadmap for the immune pathogenesis*  
40 509 *of gout*. *RMD Open*, 2015. **1**(Suppl 1): p. e000046.

- 1  
2  
3 510 47. Geng, Q., et al., *Febuxostat mitigates IL-18-induced inflammatory response and reduction*  
4 511 *of extracellular matrix gene*. Am J Transl Res, 2021. **13**(3): p. 979-987.
- 5  
6 512 48. Nasi, S., et al., *Xanthine Oxidoreductase Is Involved in Chondrocyte Mineralization and*  
7 513 *Expressed in Osteoarthritic Damaged Cartilage*. Front Cell Dev Biol, 2021. **9**: p. 612440.
- 8  
9 514 49. Li, J., Z. Zhang, and X. Huang, *L-Arginine and allopurinol supplementation attenuates*  
10 515 *inflammatory mediators in human osteoblasts-osteoarthritis cells*. Int J Biol Macromol, 2018.  
11 516 **118**(Pt A): p. 716-721.
- 12  
13 517 50. Kiltz, U., et al., *Treat-to-target (T2T) recommendations for gout*. Ann Rheum Dis, 2017.  
14 518 **76**(4): p. 632-638.
- 15  
16 519 51. Perez-Ruiz, F., et al., *Treat to target in gout*. Rheumatology (Oxford), 2018. **57**(suppl\_1):  
17 520 p. i20-i26.
- 18  
19 521 52. Miao, Z., et al., *Dietary and lifestyle changes associated with high prevalence of*  
20 522 *hyperuricemia and gout in the Shandong coastal cities of Eastern China*. J Rheumatol,  
21 523 2008. **35**(9): p. 1859-64.
- 22  
23 524 53. Lin, K.C., H.Y. Lin, and P. Chou, *The interaction between uric acid level and other risk*  
24 525 *factors on the development of gout among asymptomatic hyperuricemic men in a*  
25 526 *prospective study*. J Rheumatol, 2000. **27**(6): p. 1501-5.
- 26  
27 527 54. Hak, A.E. and H.K. Choi, *Menopause, postmenopausal hormone use and serum uric acid*  
28 528 *levels in US women--the Third National Health and Nutrition Examination Survey*. Arthritis  
29 529 Res Ther, 2008. **10**(5): p. R116.
- 30  
31 530 55. Nicholls, A., M.L. Snaith, and J.T. Scott, *Effect of oestrogen therapy on plasma and urinary*  
32 531 *levels of uric acid*. Br Med J, 1973. **1**(5851): p. 449-51.
- 33  
34 532 56. Ding, X., et al., *The associations of serum uric acid level and hyperuricemia with knee*  
35 533 *osteoarthritis*. Rheumatol Int, 2016. **36**(4): p. 567-73.
- 36  
37 534 57. Srikanth, V.K., et al., *A meta-analysis of sex differences prevalence, incidence and severity*  
38 535 *of osteoarthritis*. Osteoarthritis Cartilage, 2005. **13**(9): p. 769-81.
- 39  
40 536 58. El Miedany, Y., et al., *Incorporating patient reported outcome measures in clinical practice:*  
41 537 *development and validation of a questionnaire for inflammatory arthritis*. Clin Exp  
42 538 Rheumatol, 2010. **28**(5): p. 734-44.
- 43  
44 539 59. Murphy, L.B., et al., *Defining Arthritis for Public Health Surveillance: Methods and*  
45 540 *Estimates in Four US Population Health Surveys*. Arthritis Care Res (Hoboken), 2017.  
46 541 **69**(3): p. 356-367.
- 47  
48 542

1  
2  
3 543 **Figure legends**

4 544 **Figure 1.** Flow chart of sample selection from the NHANES 2007–2018

5  
6 545

7 546 **Supplemental appendix**

8 547 **sTable 1.** Characteristics of participants included in this study.

9 548 **sTable 2.** Subgroup analysis of the association of arthritis subtype (RA, OA, other and  
10  
11 549 unspecified) and AH.

12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

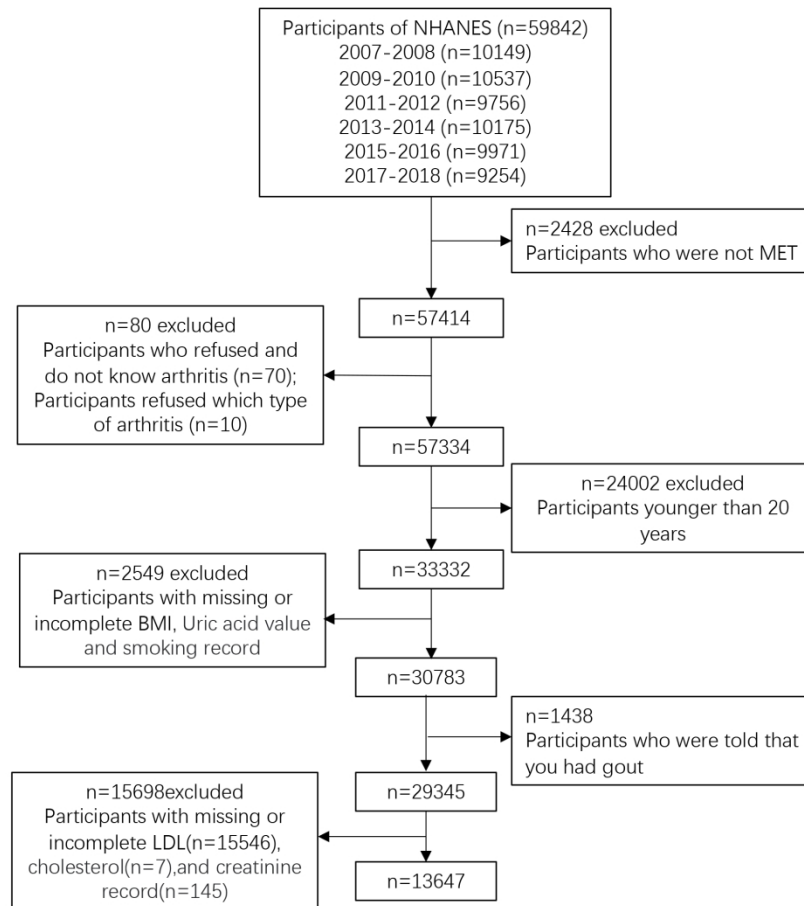


Figure 1. Flow chart of sample selection from the NHANES 2007–2018

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)	



1							
2							
3							
4							
5	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)
6							
7	Education Level						<0.01
8	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)
9	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)
10	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)
11							
12	BMI						<0.01
13							
14	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)
15	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)
16	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)
17							
18	Blood pressure						<0.01
19							
20	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)
21	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)
22							
23	PIR						<0.01
24							
25	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)
26	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)
27	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)
28							
29	Smoking						0.01
30							
31	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)
32	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)
33	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)
34							
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							

1								
2								
3								
4								
5	PAL							<0.01
6								
7	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)	
8	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)	
9								
10	Diabetes							<0.01
11								
12	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)	
13	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)	
14								
15	With or without arthritis							<0.01
16								
17	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)	
18	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)	
19								
20	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)	
21	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)	
22	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)	
23	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)	
24								
25	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
26	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
27	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
28	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
29								
30	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
31	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)
<b>Gander</b>				
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
<b>Age</b>				
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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

1	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	13-14
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5				
6				
7				
8				
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
10				
11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	15
14	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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
20				
21	<b>Other information</b>			
22	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
23				
24				

\*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>.