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The association between asymptomatic hyperuricemia and knee osteoarthritis: data from the third National Health and Nutrition Examination Survey

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SUMMARY

Objective: *In vitro* and clinical studies suggest that urate may contribute to osteoarthritis (OA) risk. We tested the associations between hyperuricemia and knee OA, and examined the role of obesity, using a cross-sectional, nationally representative dataset.
Method: National Health and Nutrition Examination Survey (NHANES) III used a multistage, stratified probability cluster design to select USA civilians from 1988 to 1994. Using NHANES III we studied adults >60 years, with or without hyperuricemia (serum urate > 6.8 mg/dL), excluding individuals with gout (i.e., limiting to asymptomatic hyperuricemia (AH)). Radiographic knee OA (RKOA) was defined as Kellgren–Lawrence grade ≥ 2 in any knee, and symptomatic radiographic knee osteoarthritis (RKOA) (sRKOA) was defined as RKOA plus knee pain (most days for 6 weeks) in the same knee.
Results: AH prevalence was 17.9% (confidence interval (CI) 15.3–20.5). RKOA prevalence was 37.7% overall (CI 35.0–40.3), and was 44.0% for AH vs 36.3% for normouricemic adults ($p = 0.056$). symptomatic radiographic knee osteoarthritis (sRKOA) was more prevalent in AH vs normouricemic adults (17.4% vs 10.9%, $p = 0.046$). In multivariate models adjusting for obesity, model-based associations between AH and knee OA were attenuated (for RKOA, prevalence ratio (PR) = 1.14, 95% CI 0.95, 1.36; for sRKOA, PR = 1.40, 95% CI 0.98, 2.01). In stratified multivariate analyses, AH was associated with sRKOA in adults without obesity (PR = 1.66, 95% CI 1.02, 2.71) but not adults with obesity (PR = 1.21, 95% CI 0.66, 2.23).
Conclusions: Among adults aged 60 or older, AH is associated with knee OA risk that is more apparent in adults without obesity.

Introduction

Osteoarthritis (OA), the most common type of arthritis worldwide[1,2], is a painful and debilitating condition for which no disease modifying therapy currently exists[3]. USA national estimates of the prevalence of radiographic knee OA (RKOA) and symptomatic radiographic knee osteoarthritis (sRKOA) were last measured in 1991–1994, revealing a prevalence of 37.4% and 12.1% respectively for adults ≥60 years[4]. Although OA was historically regarded as a disease of mechanical degeneration, it is now recognized that inflammation plays an important role in its pathogenesis[5]. Intra-articular and serum levels of pro-inflammatory mediators, including cytokines such as IL-1β, have been associated with more rapid OA progression[6].

Hyperuricemia is a chronic metabolic condition that is the necessary precursor for the development of gout, the most common inflammatory arthritis[7]. Prevalence of asymptomatic hyperuricemia (AH; hyperuricemia in the absence of gout) in the US has been increasing and is approximately 17.6%, significantly higher than the prevalence of gout (3.9%)[7]. A number of investigators have identified potential biological relationships between urate, gout

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and OA[8]. Elevated serum urate (sU) levels have been reported to promote low-level systemic inflammatory states, even in the absence of frank gout[9]. At higher concentrations, urate can crystallize as monosodium urate (MSU), stimulating the NLRP3 inflammasome and potentially promoting IL-1β production and cartilage damage[10]. We previously examined the association between sU and knee OA in a small cohort of male veterans and found that both gout and AH were associated with increased prevalence and severity of knee OA[11]. In a subsequent study, we observed that increased sU levels in patients with RKOA but no gout were associated with more rapid progression of radiographically-assessed joint space narrowing[12]. Others have noted an association between synovial fluid urate and OA severity[13]. Additionally, studies have suggested that a diagnosis of gout may be associated with an increased risk for OA[14,15]. However, in studying the relationship between gout and OA, it is difficult to distinguish between effects of hyperuricemia, gouty inflammation and extensive urate deposition, all of which are subsumed under a gout diagnosis.

To date, most studies specifically examining the relationship between hyperuricemia and OA have been based on limited numbers of subjects and/or have lacked external validity[11–13] In the current study, we used data from the large National Health and Nutrition Examination Survey (NHANES) of the United States Centers for Disease Control and Prevention (CDC) to determine the associations between AH and RKOA/sRKOA among older adults in the US. We also assessed whether obesity, an important risk factor for both knee OA and gout[16–18], confounded and/or modified these associations.

Method

Data source: NHANES is a nationally representative sample of the US non-institutionalized adult population, with both interview and examination components[19,20]. NHANES uses a multistage, stratified probability cluster design to select a representative sample of the civilian noninstitutionalized population. NHANES III, conducted between 1988 and 1994, was the most recent NHANES survey to assess knee OA using radiographs[19–21]. We chose NHANES III as our data source because 1) sU measurements were collected on all patients; 2) self-reported diagnoses of gout were collected, allowing us to distinguish between AH and gout; 3) RKOA was established based on radiographic evaluation, using a modified Kellgren–Lawrence (KL) scoring system[4] (see also "Case definition" section, below); and 4) self-reports of knee pain were collected, allowing us to assess for diagnoses of sRKOA[21]. The NHANES III survey protocol was approved by the National Center for Health Statistics Institutional Review Board and written informed consent for data collection was obtained from all participants[19,20].

Study participants: From among 33,994 participants enrolled in NHANES III we extracted data for adults age 60 and older from the study Phase II (1991–1994), because knee radiographs were read only in this subgroup[21]. These participants had been interviewed and attended Mobile Exam Centers (MECs) for X-ray and laboratory studies.

2589 participants were identified in the above initial screen. Because gout patients may have direct damage of joints from gouty disease that may confound assessment of OA[22], and additionally may experience acute episodes of pain and inflammation that do not occur in AH, we elected to study only patients with AH in order to more specifically assess the relationship between sU and OA. Patients who had answered yes to the question, "Has a doctor ever told you that you had gout?" were therefore excluded from further analysis ($n = 159$). We additionally excluded participants whose records were missing sU values ($n = 86$) and/or had radiographic data that were missing, incomplete or inadequate for evaluation ($n = 131$), resulting in an analytic sample of 2213 participants (Fig. 1). An additional five participants were excluded in the sRKOA analyses due to missing symptoms data.

Knee radiographs: Each participant underwent a single non-weight bearing bilateral anterior-posterior (AP) knee radiograph. Radiographs were reviewed first by a single CDC radiologist; if evidence of RKOA was observed, a second reader confirmed the findings. Consensus readings were conducted in the event of disagreement between the two qualified readers. Fewer than two percent of radiographs were considered unreadable due to anatomy, motion, rotation or exposure. To assess intra- and inter-reader reliability, three sets of quality control radiographs ranging from normal to advanced disease from the study population were used.

Because joint space narrowing is not reliably measured in non-weight bearing films, a KL classification system that incorporated only tibiofemoral osteophytes and joint sclerosis scores was used to assess and categorize the degree of RKOA[4]. A strong inter-rater correlation for KL scores was confirmed, as kappa coefficients (a measure of rater agreement) were high (>0.71 out of a possible 1.00). Intra-rater kappa coefficients for primary and secondary readers were also high, > 0.84 and > 0.82 respectively, for repeat KL score evaluation, confirming intra-reader reproducibility.

Case *definition of RKOA and sRKOA:* We defined RKOA as a KL score ≥2, where grade 2 indicates the presence of definite osteophytes[21]. (As noted earlier, the modified KL scale employed excluded the parameter of joint space narrowing, since the X-ray images were not obtained under weight bearing conditions and were therefore unsuitable for assessing joint space. Accordingly, KL0 = normal; KL1 = possible osteophytic lipping; KL2 = definite osteophytes; KL3 = moderate multiple osteophytes, some sclerosis and possible deformity of bony contour; KL4 = large osteophytes, severe sclerosis and definite deformity of bony contour.) Patients with knee joint replacement were also included as RKOA, since 90–95% of all knee replacements are attributable to OA[23–25] We defined sRKOA as evidence of RKOA (including KL ≥ 2 as defined above) plus a patient-reported history of persistent knee pain in the corresponding joint, obtained during household interviews. Responders were asked "Have you ever had pain in your knees on most days for at least 6 weeks, including aching and stiffness?"(19).

Hyperuricemia: Several definitions of hyperuricemia are currently employed; we chose the most physiologically relevant one, i.e., sU > 6.8 mg/dL, the saturation point at which urate may precipitate under physiological conditions[26].

Potential confounders/other variables: Potential confounders were selected because of their possible relevance to OA risk, and/or

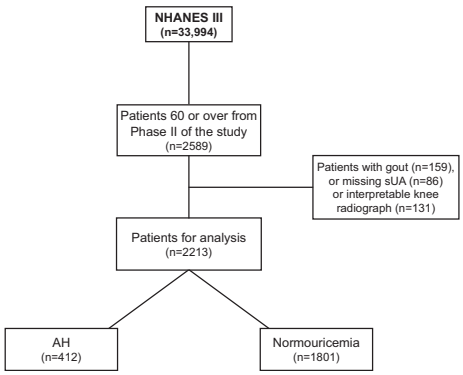

Fig. 1. Identification scheme of study participants (patients with asymptomatic hyperuricemia (AH)) using inclusion and exclusion criteria.

likely associations with AH, that could confound the association between AH and knee OA[27,28]. Demographic data were collected including self-reported sex, age, race/ethnicity, smoking, education and occupation. Age was self-reported at time of interview and categorized into three age groups: 60–69, 70–79, and ≥80 years. Self-reported race/ethnicity was coded as non-Hispanic black, non-Hispanic white, Mexican American and Other. Education was grouped as less than high school, high school, and college level. Self-reported smoking was categorized never, past, and current. Manual labor occupation was defined as the respondent's longest reported occupation equal to codes 8 and 19–40; the "Other" occupation group included all other codes. Body mass index (BMI) (kg/m^2) was calculated from measured weight and height determined by standard NHANES protocols[19,20]. Obesity status was first dichotomized, with obesity defined as BMI ≥30 kg/m^2 and without obesity as BMI <30 kg/m^2. In a secondary analysis, BMI was stratified into normal/underweight (BMI<25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), obesity class 1 (BMI 30 to <35 kg/m^2), obesity class 2 (BMI 35 to <40 kg/m^2) and obesity class 3 (BMI ≥40 kg/m^2), as per the CDC[29]. We also performed a secondary analysis to examine the effect of AH on bilateral knee OA outcomes with the intention of understanding how AH may impact OA disease severity and/or systemic distribution.

Statistical analysis: Statistical analyses were conducted using SUDAAN[30] and SAS[31]. The weighted prevalence estimates were calculated using survey sample weights, which were adjusted for differential selection probabilities, nonresponse, and noncoverage. Variances and confidence intervals (CIs) were calculated with SUDAAN statistical software, which accounted for the complex survey design. To compare whether the prevalence of knee OA outcomes and AH differed by age, sex, race/ethnicity, obesity status, smoking, occupation, and education, we used Wald Chi–Square tests.

We assessed the associations between AH and knee OA outcomes using log binomial regression models to estimate prevalence ratios (PRs) and 95% CIs. A backward stepwise elimination procedure was performed for all potential confounders in our study and $p \leq 0.05$ was used as a cut-off level for retention of covariates in the full multivariate adjusted model. We stratified by obesity status to determine whether the associations between AH and knee OA outcomes differed by obesity status. Statistical significance was determined at $p < 0.05$.

Results

The mean (SD) sU of the overall study population was 5.61 (0.04) mg/dL. The mean sU levels in the AH and normouricemic groups were 7.80 (0.07) and 5.14 (0.04) mg/dL, respectively.

Prevalence of AH overall and by study characteristics–Table I shows the prevalence of AH by selected baseline characteristics among adults aged ≥60 years. The overall prevalence of AH was 17.9% (CI 15.3–20.5%). AH prevalence was significantly greater among men than women (24.5% vs 13.3%, $p < 0.01$), and among those with obesity compared to those without obesity (27.4% vs 14.8%, $p < 0.01$). Adults who did manual labor had greater prevalence of AH when compared with other occupations (21.0% vs 15.1%, $p = 0.01$). There was no significant difference in the prevalence of AH by age, race/ethnicity, smoking status, and education.

Prevalence of RKOA and sRKOA overall and by study characteristics–Table II gives the distribution of RKOA by study characteristics and AH status. Among adults ≥60 years, the prevalence of RKOA was 37.7% (CI 35.0–40.3%). The prevalence of RKOA in women was

Table I
Distributions of baseline asymptomatic hyperuricemia (AH) by selected baseline characteristics among adults age ≥60 years — National Health and Nutrition Examination Survey (NHANES) III (phase 2), United States (1991–1994)

Baseline characteristics	AH (serum urate > 6.8 mg/dL with no gout)					
	Unweighted sample size*	Unweighted sample with AH*	Weighted sample with AH (millions)	Weighted %	95% CIs	*P*-Value†
Overall	2213	412	6.3	17.9	15.3–20.5	
Demographics						
Sex						<0.01
Male	1012	256	3.5	24.5	21.1–27.9	
Female	1201	156	2.8	13.3	10.3–16.4	
Age						0.76
60-69	998	187	3.1	17.5	13.5–21.4	
70-79	729	130	2.3	18.7	15.7–21.7	
≥80	486	95	1.0	17.3	12.7–21.8	
Race/ethnicity						0.09
Non-Hispanic white	1247	222	5.1	17.5	14.7–20.3	
Non-Hispanic black	401	98	0.6	22.5	16.6–28.4	
Mexican-American	468	78	0.2	17.8	13.4–21.1	
Other	97	17	0.4	17.1	7.6–26.5	
Education						0.44
Less than high school	1212	234	2.6	19.0	15.0–23.1	
High school	534	94	1.9	17.0	13.0–21.1	
College	467	84	1.8	17.2	13.7–20.8	
Occupation						0.01
Manual labor	1241	263	3.4	21.0	17.3–24.8	
Other occupations	960	147	2.9	15.1	12.4–17.8	
Health characteristics						
Obesity (kg/m^2)						<0.01
No (Body mass index(BMI) <30)	1656	257	3.9	14.8	12.2–17.3	
Yes (BMI ≥ 30)	554	155	2.4	27.4	22.4–32.3	
Smoking						0.06
Current	317	59	0.9	18.6	12.8–24.4	
Past	806	177	2.7	19.8	16.7–23.0	
Never	1090	176	2.7	16.0	12.4–19.7	

* Not all cells add up to 2213 or 412 owing to missing data.
† *P*-values derived from adjusted Wald chi-square test.

Table II
Distributions of baseline radiographic knee osteoarthritis (RKOA) by selected baseline characteristics among adults aged ≥60 years— NHANES III (phase 2), United States (1991–1994)

Baseline characteristics	RKOA					
	Unweighted sample size*	Unweighted sample with RKOA*	Weighted sample with RKOA (millions)	Weighted %	95% CIs	*P*-Value†
Overall	2213	937	13.3	37.7	35.0–40.3	
Demographics						
Sex						0.01
Male	1012	351	4.5	31.3	26.4–36.2	
Female	1201	586	8.8	42.1	37.8–46.3	
Age						<0.01
60-69	998	346	5.6	31.7	27.8–35.6	
70-79	729	338	4.8	39.8	35.0–44.6	
≥80	486	253	2.9	51.9	45.6–58.3	
Race/ethnicity						<0.01
Non-Hispanic white	1247	502	10.6	36.3	33.4–39.3	
Non-Hispanic black	401	209	1.4	52.5	46.8–58.1	
Mexican-American	468	187	0.4	40.3	32.5–48.1	
Other	97	39	0.9	36.6	26.4–46.7	
Education						<0.01
Less than high school	1212	555	6.0	43.3	39.8–46.9	
High school	534	218	3.9	35.2	29.3–41.2	
College	467	164	3.4	32.8	26.7–37.8	
Occupation						0.03
Manual labor	1241	548	6.6	41.0	37.0–45.1	
Other occupations	960	384	6.6	35.0	31.3–38.7	
Health characteristics						
Obesity Status						<0.01
Without obesity (<30 kg/m^2)	1656	598	8.3	31.3	27.3–35.4	
With obesity (≥30 kg/m^2)	554	338	4.9	57.3	51.6–63.0	
Smoking						0.01
Current	317	103	1.3	28.0	18.2–37.9	
Past	806	298	4.7	34.1	28.4–39.7	
Never	1090	536	7.3	43.3	39.1–47.5	
Asymptomatic hyperuricemia						0.056
Yes	412	191	2.8	44.0	37.1–50.9	
No	1801	746	10.5	36.3	33.2–39.4	

* Not all cells add up to 2213 or 937 owing to missing data.
† *P*-values derived from adjusted Wald chi-square test.

significantly greater than in men (42.1% vs 31.3%, $p < 0.01$). The prevalence of RKOA differed significantly by age, race/ethnicity, education, occupation, and smoking status. The prevalence of RKOA was significantly higher among adults with obesity vs adults without obesity (57.3% vs 31.3%, $p < 0.01$).

Among all adults with RKOA, 32.1% reported a history of persistent knee pain. The prevalence of sRKOA in the total study population was therefore 12.1%. The prevalence of sRKOA differed significantly by age, race/ethnicity, and was higher among adults with obesity vs adults without obesity (22.9% vs 8.5%, $p < 0.01$) (Table III).

The unadjusted prevalence of RKOA was higher for AH than for normouricemic adults, approaching statistical significance (44.0% vs 36.3%, $p = 0.056$), representing a 21% greater prevalence in the AH group (Table II). The unadjusted prevalence of sRKOA among the AH group compared with normouricemic controls was 17.4% compared with 10.9%, respectively, $p = 0.04$, representing a 64 % greater prevalence in the AH group (Fig. 2).

Multivariate analysis

Table IV shows the overall association between AH, and RKOA and sRKOA, in multivariate log binomial models. In the age-adjusted model, the prevalence ratio (PR) for RKOA and sRKOA were significantly higher in the AH group compared with the normouricemic controls (PR 1.21 (95% CI, 1.01, 1.45) for RKOA, and PR 1.59 (1.10, 2.31) for sRKOA). After further adjusting for age, sex, race/ethnicity and education, the associations between AH and RKOA and sRKOA remained significant. In this model, patients with AH were 26% more likely to have RKOA (PR 1.26, (1.06, 1.50)) and 69% more likely to have sRKOA (PR 1.69, (1.19, 2.42)) than normouricemic controls. However, in the full multivariate models (which included obesity status and excluded smoking and occupation after backward stepwise elimination), the PRs for RKOA and sRKOA were attenuated (PR 1.14 (0.95, 1.36) for RKOA, and PR 1.40 (0.98, 2.01) for sRKOA), suggesting that obesity status confounded the association between AH, and RKOA and sRKOA in adults aged 60 and older.

Association between AH and RKOA/sRKOA by obesity status—Among adults with obesity, unadjusted RKOA (58.4% vs 54.3%, $p = 0.53$) and sRKOA prevalence (26.4% vs 21.6%, $p = 0.55$) did not significantly differ between individuals with and without AH. In contrast to the finding among those with obesity, the associations of AH with RKOA and sRKOA in adults without obesity were borderline significant or significant, with PR for RKOA of 1.31 (0.98, 1.77), and PR for sRKOA of 1.66 (1.02, 2.71), after adjusting for age, sex, race/ethnicity and education in the full multivariate models.

In a secondary analysis, we examined the impact of AH on knee OA in full multivariate models according to individual subcategories of BMI. In these analyses, we found no difference in the impact of AH on RKOA between individuals who were normal weight/underweight (PR:1.24 (95% CI: 0.66, 2.36) compared with those who were overweight (PR: 1.29 (95% CI: 0.91, 1.84), and similarly found no difference when comparing between obesity class I (PR: 0.97 (95% CI: 0.77, 1.84), and II (PR: 0.97 (95% CI: 0.55, 1.65). Interestingly, among individuals with obesity class III the

Table III
Distributions of baseline symptomatic radiographic knee osteoarthritis (sRKOA) by selected baseline characteristics among adults age ≥60 years— NHANES III (phase 2), United States (1991–1994)

Baseline characteristics	sRKOA					
	Unweighted sample size*	Unweighted sample with sRKOA*	Weighted sample with sRKOA (millions)	Weighted %	95% CIs	*P*-Value†
Overall	2208	328	4.3	12.1	10.3–13.8	
Demographics						
Sex						0.08
Male	1011	118	1.4	6.6	6.6–12.9	
Female	1197	210	2.8	13.7	11.1–16.2	
Age						0.03
60-69	995	125	1.7	9.7	7.8–11.6	
70-79	728	114	1.6	13.1	10.0–16.2	
≥80	485	89	1.0	17.2	10.8–23.6	
Race/ethnicity						<0.01
Non-Hispanic white	1244	162	3.4	11.7	9.7–13.7	
Non-Hispanic black	399	74	0.5	19.2	15.3–23.2	
Mexican-American	468	81	0.1	15.6	9.6–21.6	
Other	97	11	0.2	7.4	2.2–12.6	
Education						0.21
Less than high school	1209	208	1.9	43.3	39.8–46.9	
High school	533	63	1.1	35.2	29.3–41.2	
College	466	57	1.3	32.8	26.7–37.8	
Occupation						0.09
Manual labor	1239	203	2.2	13.9	11.3–16.4	
Other occupations	957	124	2.0	10.7	8.1–13.3	
Health characteristics						
Obesity Status						<0.01
Without obesity (<30 kg/m^2)	1651	179	2.3	8.5	6.9–10.1	
With obesity (≥30 kg/m^2)	554	148	2.0	22.9	17.9–28.0	
Smoking						0.35
Current	316	32	0.5	9.5	4.4–14.6	
Past	803	114	1.6	11.6	8.9–14.3	
Never	1089	182	2.2	13.2	10.1–16.2	
Asymptomatic hyperuricemia						0.04
Yes	412	73	1.1	17.4	11.3–23.5	
No	1796	255	3.2	10.9	9.2–12.6	

* Not all cells add up to 2213 or 937 owing to missing data.
† *P*-values derived from adjusted Wald chi-square test.

impact of AH on knee OA appeared to be possibly protective for RKOA (PR: 0.46 (95% CI: 0.19, 1.10)). We note that the smaller groups involved in these RKOA subanalyses limited the statistical power of the comparisons. For sRKOA, the association with AH was most robust for normal weight/underweight: (PR: 2.44 (95% CI: 0.95, 6.24)) individuals and slightly elevated for overweight PR: 1.27 (95% CI: 0.79, 2.06) individuals. Comparing obesity classes for sRKOA was not possible given very low statistical power (as a result of the lower prevalence of sRKOA compared with RKOA), which yielded wide CIs after stratification by obesity class.

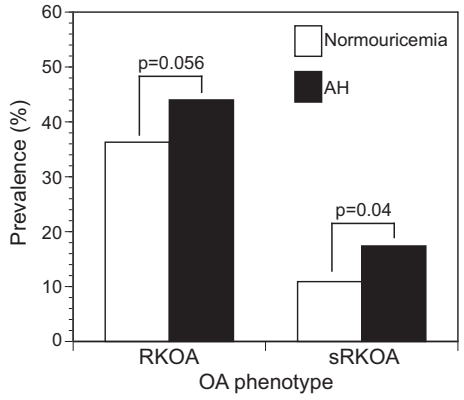

Fig. 2. Prevalence ratios of Radiographic knee OA (RKOA) and symptomatic RKOA (sRKOA) among adults aged 60 years or older with AH vs normouricemia.

In full multivariate models, the magnitude of the associations between AH and bilateral knee outcomes were similar to analyses which included all participants with knee OA. Almost 70% of individuals with AH and RKOA, and 44% of individuals with AH and sRKOA, had bilateral knee OA. Statistical power was insufficient to evaluate whether the association between AH and knee OA differed by numbers of knees with OA.

Discussion

To our knowledge, this is the first study to examine the association between AH and knee OA in a nationally representative sample. In the overall US population age over 60 years, the significant associations between AH and knee OA outcomes were attenuated by adjusting for obesity status, but remained borderline significant. In stratified analyses, AH was associated with an increased prevalence of sRKOA in adults without obesity, suggesting a potential relationship between AH and knee OA in this population. Obesity status appeared to both confound and modify associations between AH and knee OA outcomes. In epidemiology, a single variable can both confound (attenuate or augment an association between an exposure and outcome) and act as an effect modifier (meaning the association between an exposure and outcome differ by different levels of a third variable (i.e., obesity status in this Case).

Several cohort and population studies have demonstrated associations between gout and OA[11,14,15] implying a possible role for hyperuricemia. Additionally, a number of smaller studies have

Table IV
The association between AH and Radiographic knee OA (RKOA) and symptomatic RKOA (sRKOA), overall and by obesity status among adults aged ≥60 years— NHANES III (phase 2), United States (1991–1994)

	RKOA* PR (95% CI)	sRKOA* PR (95% CI)
Overall		
Age-adjusted	**1.21 (1.01, 1.45)**	**1.59 (1.10, 2.31)**
Age, sex, race/ethnicity, and education adjusted	**1.26 (1.06, 1.50)**	**1.69 (1.19, 2.42)**
Full MV model†	1.14 (0.95, 1.36)	1.40 (0.98, 2.01)
With obesity		
Age-adjusted	0.91 (0.73, 1.15)	1.19 (0.64, 2.22)
Full MV model†	0.95 (0.75, 1.19)	1.21 (0.66, 2.23)
Without obesity		
Age-adjusted	1.25 (0.93, 1.67)	1.50 (0.93, 2.44)
Full MV model†	1.31 (0.98, 1.77)	**1.66 (1.02, 2.71)**

AH, asymptomatic hyperuricemia; RKOA, radiographic knee osteoarthritis; sRKOA, symptomatic RKOA; PR, prevalence ratio; CI, confidence intervals; MV; multivariable.

* The reference group comprises participants without AH.

† A backward stepwise elimination procedure was performed with all potential confounders in our study considered and $p \leq 0.05$ was used as a cut-off level for retention of covariates in the full multivariate adjusted model. For the full MV model, the covariates retained were age, sex, race/ethnicity, education and obesity status. Stratified models by obesity status retained the same variables with the exception of obesity status, which was not considered, because it was a stratification variable.

looked at hyperuricemia *per se* and identified a possible relationship between sU and OA prevalence and/or progression[11,12]. Most recently a cross-sectional study reported a positive association between elevated sU level and knee osteophytes among women, but the investigators did not specify whether gout patients were excluded[15]. In contrast, ours is the first large study to show the associations between AH, RKOA and sRKOA.

In the overall population, we found a 26% increased prevalence of RKOA, and a remarkable 69% increased prevalence of sRKOA, among participants with AH compared with a normouricemic control population, after controlling for risk factors potentially affecting both hyperuricemia and OA, including age, sex, race/ethnicity and education[32–34]. These findings suggested a possible independent relationship between AH and knee OA. After adjusting for obesity status, the association between AH and KOA was attenuated but remained nearly significant especially among the sRKOA participants. This suggests that obesity status is likely a confounder of the relationship between AH and OA in the overall population, but that there is still a potential, albeit attenuated, independent effect of AH on knee OA.

When stratifying by obesity status, we found no significant association between AH, and RKOA and sRKOA, amongst adults with obesity. In contrast however, the associations between AH and RKOA or sRKOA were significant or nearly significant among adults without obesity. These observations were confirmed in a separate analysis of individual BMI categories and suggest that while obesity status may modify the impact of AH on knee OA, AH is likely to be an independent risk factor that is apparent among older adults without obesity. Such an interpretation is consistent with a prior report that an association between AH and knee OA was attenuated by obesity[11], and with a report that whereas lean women with gout were more likely to undergo knee arthroplasty for severe OA than lean women without gout, this relationship did not hold for heavier women[35]. In this context it is also noteworthy that a recent report from our group, indicating a relationship between sU and OA, limited its subjects to a maximal BMI of <33[12]. The relationship between obesity and sU in OA is undoubtedly complex, since obesity is a risk factor for both OA[36] (owing to mechanical joint stress and/or systemic metabolic effects) and hyperuricemia[37] (owing to common dietary features and/or systemic metabolic effects). Thus, the direct impact of obesity on OA may simply overwhelm that of sU, or obesity may additionally be a marker for higher sU levels with their own independent effects. In either case, the persistence of increased OA risk among AH patients without obesity suggests that when present, hyperuricemia is likely to contribute to OA risk.

We further observed that the impact of an elevated sU level on knee OA was even more strongly associated with the presence of OA knee pain (i.e., sRKOA) among adults without obesity and specifically among those individuals who were normal weight/underweight. This finding suggests patients with higher sU level may be at risk for more severe disease[38], and raises the question of whether urate is involved in OA pathogenesis. Several *in vitro* studies indicate that exposure to urate may have adverse effects on chondrocytes that mimic intrinsic OA processes[13,39]. Additionally, synovitis is increasingly appreciated as a common feature in OA, which associates with both pain and OA progression[40]. Consistent with a possible relationship between sU and synovitis in OA, we have reported that elevated sU levels distinguish OA progressors and non-progressors, and that sU levels associate with MRI-based synovitis in these subjects[12].

Strengths and novelties of our study include a large sample size, the use of nationally representative data, the elimination of gout patients and the focus exclusively on the impact of non-gout hyperuriciema, as well as the use of objective and validated measurements of AH and knee OA. Our study also had several limitations. We were unable to consider the question of causality, given the cross-sectional methodology we employed. Additionally, because diagnoses of gout and some potential confounders were self-reported, inaccuracies in the capture of these clinical features may have occurred. Our use of BMI to define obesity/non-obesity may obscure more subtle distinctions in terms of the physiologic processes of obesity, but is supported by numerous other studies using high BMI as an obesity surrogate. Our use of a population over the age of 60 may limit the generalizability of our data, although the majority of patients with knee OA are over 60[27]. Our use of total knee replacement (TKR) as a surrogate for knee OA may have led us to include some patients who underwent knee replacement for a different indication, but over 90% of knee replacements are for OA in adults over age 50[25,41], and only a small minority (3.8%) of our patients were diagnosed with knee OA on the basis of TKR. Because NHANES collected only AP Xray images, no inference can be made regarding the relationship of AH to patellofemoral OA. Moreover, the dataset lacked information that would allow us to identify whether the medial or lateral compartment of the OA knees were affected, an important consideration since while knee OA is 3–4 fold more common in the medial compartment, different risk factors appear to be related more strongly with one compartment or

the other (e.g., obesity is more strongly associated with medial disease, whereas female sex may be more strongly associated with lateral disease)[42]. One issue of possible concern is our use of the older NHANES III dataset rather than a more recent NHANES survey. As noted earlier however, our choice was predicated on the fact that NHANES III is the most recent NHANES dataset that includes all the data needed for our analyses. Moreover, since 1) no distinctly new treatment modalities for OA have come into use since NHANES III, 2) the management of AH has also not changed (i.e., treatment of AH continues to be not endorsed in U.S. guidelines[43]), and 3) prevalences of AH, OA and obesity appear to have risen in parallel in the past several decades[44,45], conclusions derived from NHANES III are likely to remain relevant, and to speak to the need for new knowledge and modern therapies.

In conclusion, our results indicate that AH is associated with an increased prevalence of sRKOA in adults without obesity and a borderline association in all adults aged 60 years or older, suggesting that urate may play a role in OA pathogenesis and/or serve as a biomarker of more severe and painful disease.

Declaration of authors' contributions

All authors made substantial contributions to the manuscript, including conception and design, preparing the manuscript, and approving the final version.

Shudan Wang, MD—Conception and design of study, data analysis and interpretation; writing the first draft and participating in revision; and approving the final version.

Michael H Pillinger, MD—Conception and design of study, data interpretation; drafting and revising the manuscript; and approving the final version.

Svetlana Krasnokutsky, MD, MS—Design of study, data interpretation; revising the manuscript, and final approval.

Kamil Barbour, PhD, MPH, MS—Conception and design of study, data accession, analysis and interpretation; revision of manuscript; and approving the final version.

Competing interests

None of the authors report any directly competing interests for the current study. For the purposes of full disclosure, MHP serves/has served as a consultant for AstraZeneca, Crealta, Horizon, Ironwood and SOBI, and as a site investigator for the Takeda-sponsored CARES study. SK has served as a consultant for Crealta, Horizon and Ironwood.

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CDC disclaimer

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