Sleep and Breathing (2019) 23:1047–1057
https://doi.org/10.1007/s11325-019-01827-1

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

A meta-analysis of the association between gout, serum uric acid level, and obstructive sleep apnea

Tingting Shi[1] · Min Min[1] · Chenyu Sun[2] · Ce Cheng[3] · Yun Zhang[1] · Mingming Liang[1] · Feras Kamel Rizeq[4] · Yehuan Sun[1,5]

Received: 23 January 2019 / Revised: 23 February 2019 / Accepted: 9 March 2019 / Published online: 22 March 2019

Abstract

Previous epidemiological investigations have evaluated the association between gout, serum uric acid levels, and obstructive sleep apnea syndrome (OSAS), but with inconsistent results. We conducted this meta-analysis aiming at providing clear evidence about whether OSAS patients have higher serum uric acid levels and more susceptible to gout. Relevant studies were identified via electronic databases from inception to December 17, 2018. Study selection was conducted according to predesigned eligibility criteria, and two authors independently extracted data from included studies. The hazard ratio (HR) and weighted mean difference (WMD) and their corresponding 95% confidence interval (CI) were derived using random-effects models. We conducted meta-, heterogeneity, publication bias, sensitivity, and subgroup analyses. Eighteen studies, involving a total of 157,607 individuals (32,395 with OSAS, 125,212 without OSAS) and 12,262 gout cases, were included. Results show that serum uric acid levels are elevated in patients with OSAS (WMD = 52.25, 95% CI 36.16–64.33); OSAS did not reach statistical significance as a predictor of gout (but there was a trend, HR = 1.25, 95% CI 0.91–1.70) and that the association between OSAS and serum uric acid was quite robust. OSAS may be a potential risk factor for hyperuricemia and the development of gout and thus, effective OSAS therapy may present as a valuable preventive measure against gout. Still, it is vital to undertake clinical studies with better designing to corroborate these associations and shed new light on it.

Keywords Obstructive sleep apnea syndrome · OSAS · Serum uric acid level · Gout

Introduction

Gout is the most prevalent inflammatory arthropathy, which affects approximately 1.4% of adults [1, 2] and has increased over the past few decades to 3.9% and 2.5% in the USA and the UK respectively [3, 4]. Similar trends have also been reported in other countries [5–7]. Gout is the most painful form of acute arthritis accompanied by considerable comorbidity including the metabolic syndrome, insulin resistance, hypertension, obesity, and

✉ Yehuan Sun
yhsun_ahmu_edu@yeah.net

Tingting Shi
shitingting199205@163.com

Min Min
419023179@qq.com

Chenyu Sun
drsunchenyu@yeah.net

Ce Cheng
ccheng19@midwestern.edu

Yun Zhang
1476920440@qq.com

Mingming Liang
840541969@qq.com

Feras Kamel Rizeq
ferisvanatari@gmail.com

[1] Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

[2] The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, China

[3] Arizona College of Osteopathic Medicine, Midwestern University, 19555 N 59th Ave, Glendale, AZ 85308, USA

[4] Avalon University School of Medicine, Santa Rosaweg 122-124, Willemstad, Curaçao

[5] Center for Evidence-Based Practice, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

particularly cardiovascular disease [8–13]. In addition, recent prospective epidemiological studies have suggested that gout confers additional independent cardiovascular risk after adjustment for traditional risk factors [14, 15].

Obstructive sleep apnea (OSA) is characterized by recurrent hypopnea or apnea during sleep, which results in intermittent hypoxia or sleep fragment; OSA affects 2–4% of the world's population [16]. Similar to gout, obstructive sleep apnea syndrome (OSAS) is also related to the abovementioned comorbidity burdens (the metabolic syndrome, obesity, hypertension, hyperlipidemia, diabetes mellitus, and cardiovascular disease) [17–23].

First, studies have shown an increased prevalence of metabolic syndrome in OSAS patients [18] and individual components of the metabolic syndrome such as hypertension, obesity, and diabetes mellitus are recognized to be independent risk factors for the development of gout [24]. Second, evidence also suggested that elevated serum uric acid levels, the most important pathophysiological basis for gout, are also frequently identified in patients with OSAS [25]. However, it is less widely recognized, only one-quarter to one-half of patients with OSAS have been shown to have hyperuricemia [21, 25–27]. There are also studies that clearly suggest that high uric acid levels are an independent risk factor for cardiovascular diseases [28, 29]. Kim et al. [28] pointed out in a meta-analysis that the risk of death from coronary heart disease increased by 12% for every 1 mg/dL increase in blood uric acid levels. Krishnan et al. [29] pointed out that hyperuricemia is an independent risk factor for atherosclerosis in a cross-sectional study of 2498 adults. Third, Choi et al. reported that gout attacks 2.4 times higher during the night than in the daytime [30]. Among several explanations that have been postulated as a possible cause of this nocturnal risk, one is the potential role of sleep apnea, which is common among obese with multiple comorbidities, a typical profile of gout patients [31–34]. Furthermore, several prospective cohort studies that directly investigated the association between OSAS and gout were recently published, but with inconsistent conclusions.

On account of all aforementioned, both hyperuricemia and gout are risk factors for cardiovascular diseases; OSAS might be associated with both hyperuricemia and gout. However, to the best of our knowledge, no systematical analysis has been conducted to explore the direct association between OSAS and gout and also, no systematical analysis for the association between OSAS and serum uric acid level. Therefore, we undertook this meta-analysis to clarify these two associations.

Materials and methods

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement and checklist were followed as much as possible during this review [35].

Search strategy

PubMed, Cochrane Library, Web of science, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database, and Wanfang (Chinese) were searched for relevant studies from inception to December 2018, using the following terms and their combinations: obstructive sleep apnea OR OSA OR obstructive sleep OR apnea-hypopnea syndrome OR OSAHS OR sleep apnea OR obstructive sleep apnea syndrome OR OSAS OR obstructive sleep hypopnea OR sleep-disordered breathing OR upper airway resistance; uric acid OR uric acid levels OR UA OR serum uric acid OR SUA OR hyperuricemia; and gout OR gouty OR arthritis OR gouty arthritis. We supplemented the computerized search by a manual search of the bibliographies of all retrieved articles for further relevant publications. No restrictions were imposed on the time of publication and language.

Selection criteria

Two independent reviewers identified the selected studies. The studies were deemed eligible if they satisfied the following criteria: (1) all participants were examined by polysomnography (PSG) and participants were assigned into two groups according to their apnea-hypopnea index (AHI) values (OSAS group, AHI $\geq$ 5; control group, AHI $<$ 5); (2) serum uric acid levels were measured from morning fasting venous blood; (3) gout cases were diagnosed by a physician or were accompanied by a prescription of anti-hyperuricemic drugs; (4) the subjects did not receive any treatments, such as CPAP treatment and operations; (5) the study provided sufficient data that for a meta-analysis. A study was excluded if information available was not adequate for data extraction; besides, abstract, letters to the editor, and case reports were not included.

Two authors (T Shi and M Min) independently did the eligibility assessment and discrepancies were resolved through discussion.

Data extraction and assessment of study quality

The following information was abstracted according to predesigned data extraction form by two independent authors: first author, year of publication, location, OSAS severity, sample size, mean age, mean BMI and serum uric acid levels in both groups, and another reviewer checked the extracted data for completeness and accuracy. The quality assessment of included studies was performed using the Newcastle-Ottawa Quality Assessment Scale (NOS). Relevant details were shown in Table 1.

Table 1 Characteristics of eligible studies included in this meta-analysis on OSA and serum uric acid level

Author	Year	Country	OSAS severity	UA (OG, μmol/L)			UA (CG, μmol/L)			Mean age (year)		Mean BMI (kg/m^2)		Mean AHI (events/h)	
				Mean1	SD 1	Total 1	Mean 2	SD 2	Total 2	Age OG	Age CG	BMI OG	BMI CG	AHI OG	AHI CG
Xu Y	2010	China	Mild	280.69	51.37	20	252.05	42.49	20	57.7	58.3	27.93	27.57	NA	NA
Xu Y	2010	China	Moderate	392.37	44.62	22	252.05	42.49	20	57.7	58.3	27.93	27.57	NA	NA
Xu Y	2010	China	Severe	423.28	58.48	22	252.05	42.49	20	57.7	58.3	27.93	27.57	NA	NA
Liu MQ	2013	China	Mild	274.31	34.25	32	259.33	31.45	35	5.1	5.5	15.90	15.20	9.3	2.42
Liu MQ	2013	China	Moderate	302.49	35.46	41	259.33	31.45	35	5.8	5.5	16.20	15.20	22.46	2.42
Liu MQ	2013	China	Severe	327.67	39.57	25	259.33	31.45	35	6.1	5.5	16.70	15.20	56.4	2.42
Deng QF	2011	China	Mild	244	47	25	229	39	30	4.2	3.9	16.70	16.20	9.2	2.6
Deng QF	2011	China	Moderate	251	52	43	229	39	30	4.2	3.9	16.60	16.20	21.5	2.6
Deng QF	2011	China	Severe	272	56	29	229	39	30	4.2	3.9	17.00	16.20	57.6	2.6
Deng KP	2007	China	Mild	262.87	92.06	28	252.05	75.64	43	43.56	38.21	25.13	23.43	10.2	2.42
Deng KP	2007	China	Moderate	286.14	138.93	25	252.05	75.64	43	43.56	38.21	26.68	23.43	29.48	2.42
Deng KP	2007	China	Severe	366.79	92.69	46	252.05	75.64	43	43.56	38.21	28.55	23.43	61.32	2.42
Zhang XY	2008	China	Mild	392.1	88.22	32	304.36	80.12	23	43.1	46	NA	NA	NA	NA
Zhang XY	2008	China	Moderate	460.14	118.86	46	304.36	80.12	23	45.6	46	NA	NA	NA	NA
Zhang XY	2008	China	Severe	537.63	134.11	56	304.36	80.12	23	47.6	46	NA	NA	NA	NA
Ruiz García	2006	Spain	Mild	359.98	90.44	151	358.79	95.2	281	52	52	32.40	32.40	NA	NA
Ruiz García	2006	Spain	Moderate	370.69	91.63	355	358.79	95.2	281	52	52	32.40	32.40	NA	NA
Ruiz García	2006	Spain	Severe	400.44	89.85	348	358.79	95.2	281	52	52	32.40	32.40	NA	NA
Zhang LF	2015	China	Mild	358.96	74.58	19	339.74	90.13	8	47.21	39.38	25.52	24.94	9.3	2.42
Zhang LF	2015	China	Moderate	399.87	90.14	24	339.74	90.13	8	44	39.38	27.21	24.94	22.46	2.42
Zhang LF	2015	China	Severe	445.2	99.55	53	339.74	90.13	8	42.55	39.38	28.07	24.94	56.4	2.42
Sunnetcioglu	2017	Turkey	Mild	351.05	83.3	149	345.1	77.35	197	44.5	40	30.10	28.30	9.2	2.6
Sunnetcioglu	2017	Turkey	Moderate	357	77.35	98	345.1	77.35	197	48.7	40	32.00	28.30	21.5	2.6
Sunnetcioglu	2017	Turkey	Severe	380.8	83.3	156	345.1	77.35	197	48.5	40	33.00	28.30	57.6	2.6
Ding SF	2009	China	Mild	365.3	92.37	27	336.81	74.07	20	54.93	50.9	28.52	26.92	10.2	2.42
Ding SF	2009	China	Moderate	374.63	78.17	19	336.81	74.07	20	57.68	50.9	29.07	26.92	29.48	2.42
Ding SF	2009	China	Severe	440.26	92.14	34	336.81	74.07	20	51.38	50.9	31.66	26.92	61.32	2.42
Ding SF	2009	China	OSAS	399.37	94.92	80	336.81	74.07	20	54.08	50.9	29.99	26.92	NA	NA
Huang ZY	2011	China	Mild	264	79.26	83	268	61.48	65	4	4	15.70	15.20	NA	NA
Huang ZY	2011	China	Moderate	251	55.19	29	268	61.48	65	4	4	15.60	15.20	NA	NA
Huang ZY	2011	China	Severe	233	87.41	26	268	61.48	65	4	4	15.50	15.20	NA	NA
Huang ZY	2011	China	OSAS	254	69.48	138	268	61.48	65	4	4	15.70	15.20	NA	NA
Wu J	2008	China	M-M	316.1	80.75	20	310.32	57.44	22	43.67	46	27.64	21.96	53.94	NA

Table 1 (continued)

Author	Year	Country	OSAS severity	UA (OG, μmol/L)			UA (CG, μmol/L)			Mean age (year)		Mean BMI (kg/m^2)		Mean AHI (events/h)	
				Mean1	SD 1	Total 1	Mean 2	SD 2	Total 2	Age OG	Age CG	BMI OG	BMI CG	AHI OG	AHI CG
Wu J	2008	China	Severe	381.41	75.72	64	310.32	57.44	22	46.05	46	25.21	21.96	53.94	NA
Wu J	2008	China	OSAS	373.32	84.69	84	310.32	57.44	22	42.92	46	28.41	21.96	53.94	NA
Yi XB	2010	China	M-M	316.1	80.75	50	310.32	57.44	62	46.05	44.1	25.21	21.96	27.75	NA
Yi XB	2010	China	Severe	381.41	75.72	18	310.32	57.44	62	42.92	44.1	28.41	21.96	62.12	NA
Yi XB	2010	China	OSAS	373.32	84.69	68	310.32	57.44	62	43.67	44.1	26.64	21.96	NA	NA
Li p	2009	China	OSAS	340.81	70.56	31	295.41	72.14	20	49	48	NA	NA	NA	NA
Hira	2012	India	OSAS	455.77	124.95	40	315.35	85.09	40	45	45	35.00	35.00	NA	NA

OSAS, obstructive sleep apnea syndrome; *NA*, not available; *OG*, obstructive sleep apnea syndrome group; *CG*, control group; *SD*, standard deviation; *M-M*, mild-severe OSAS; *M/S*, mild/severe OSAS; *BMI*, body mass index; *AHI*, apnea-hypopnea index

Statistical analysis

We estimated pooled HRs with 95% CIs for binary outcomes and WMDs with 95% CI for continuous outcomes. Mantel-Haenszel analysis was utilized for dichotomous variables and the inverse variance method was used for continuous variables [36]. Moreover, we also stratified the data into subgroups based on OSAS severity (mild, moderate, severe): age (≦ 15 and > 15); BMI (underweight, normal weight, overweight, obesity; for studies from China, we define normal weight as 18.5–23.9 kg/m^2, overweight as BMI ≧ 24 kg/m^2, and obesity as BMI ≧ 28 kg/m^2; for studies from other countries, we have adopted WHO recommended standards (defines normal weight as 18.5–24.9 kg/m^2, overweight as BMI ≧ 25 kg/m^2, and obesity as BMI ≧ 30 kg/m^2)) [37]; and AHI (≧ 30 and < 30), respectively. The subgroup data were analyzed separately. Possible heterogeneity between studies was investigated using the Q test and I^2 statistic. The existence of significant heterogeneity necessitated the use of a random-effects model; otherwise, a fixed effects model was used. Begg's and Egger's tests were conducted to assess publication bias. To weigh the influence of each eligible study on the pooled estimate and to assess the robustness of results from our meta-analysis, a sensitivity analysis was performed by omitting one study at each turn. All statistical analyses were implemented in Stata version 14.0 (Stata, version 14; Stata Corp, College Station, TX, USA). The difference was considered statistically significant when $p < 0.05$.

Results

Study selection and characteristics of eligible studies

After initial systematical search and supplementary search, a total of 1191 records were identified. Three hundred twenty-six articles were excluded by browsing the title and abstract. Then, another 33 articles were excluded for reasons shown in Fig. 1. After a thorough discussion between the two reviewers, a total of 18 studies were finally included in our meta-analysis. The detailed steps of the literature search are shown in Fig. 1.

The characteristics of the included studies were detailed in Tables 1 and 2. The 18 included articles were published from 2006 to 2018. Of these, 14 were for the association between OSAS and serum uric acid level [25, 38–50], 11 of the 14 studies were conducted in China, and the remaining three were one each in Indian, Spain, and Turkey. Four (3 cohort studies and 1 cross-sectional study) were for the association between OSAS and gout [51–54]. Among them, three were conducted in the UK and one in Taiwan of China.

Association between OSAS and serum uric acid level

Fourteen studies [25, 38–50], involving a total of 5219 individuals (2656 with OSAS, 2563 without OSAS), were identified and included for the association between OSAS and Serum uric acid level. Eight of these studies [25, 39–42, 45, 48, 49] investigated OSAS in three different groups (mild OSAS, moderate OSAS, severe OSAS), two investigated in another three different groups (mild-moderate OSAS, severe OSAS, all OSAS) [44, 46], two [43, 47] investigated OSAS in four different groups (mild OSAS, moderate OSAS, severe OSAS, and all OSAS), and the data were analyzed separately for each group. The remaining two studies only reported data for all OSAS and control groups and analyzed each as a single study [38, 40]. In summary, a total of 40 subgroups were analyzed in our analysis (Tables 1 and 2).

Pooled analysis

The overall pooled results were presented in Fig. 2, which indicated that serum uric acid levels in OSAS group were higher than control groups (WMD = 50.25, 95% CI 36.16–64.33, $p = 0.000$)). Significant heterogeneity was observed between the studies ($I^2 = 91.2\%$), suggesting that it was imperative to conduct subgroup analysis.

Subgroup analysis: OSAS severity

Mild OSAS: pooled WMD in a subgroup of mild OSAS was 14.62 (95% CI 3.18–26.05, $p = 0.054$). In the meantime, the total WMD of the subgroup with moderate and severe was more significant, with a value of 47.75 (95% CI 18.43–77.08, $p = 0.000$) and 82.87 (95% CI 53.00–112.74, $p = 0.000$) respectively. Pooled WMD in a subgroup of all OSAS was 57.93 (95% CI 16.49–99.37, $p = 0.000$) (Fig. 3).

Subgroup analysis: age

Age > 15: the total WMD in the studies with an average age beyond 15 was significant, with a corresponding value of 63.96 (95% CI 46.13–81.79, $p = 0.000$). Age ≦ 15: the total WMD in the studies with an average age less than 15 was not significant, with a corresponding value of 14.55 (95% CI − 5.71–34.81, $p = 0.000$) (Fig. 3).

Subgroup analysis: BMI

Underweight: the pooled WMD was 15.04 (95% CI − 3.63–33.70, $p = 0.000$). Overweight: the pooled WMD was 57.05 (95% CI 20.47–93.64, $p = 0.000$). Obesity: the pooled WMD was 49.92 (95% CI 32.27–67.57, $p = 0.000$). BMI not available: the pooled WMD was 129.87 (95% CI 49.07–210.68, $p = 0.000$) (Fig. 3).

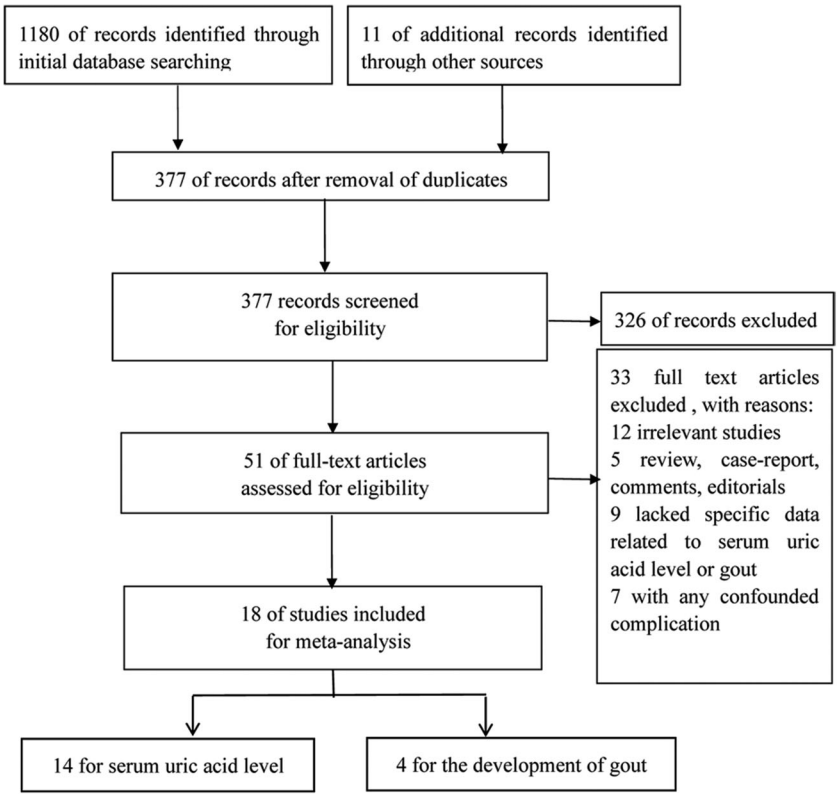

Fig. 1 Flow diagram of the study search selection process

Table 2 Characteristics of eligible studies included in this meta-analysis on OSAS and gout

First author	Year	Country	Design	Statistical methods	Follow-up (years)	Age (years, mean (SD))		Sample size		The number of gout		HR (95% CI)	Study quality
						SA	Non-SA	SA	Non-SA	SA	Non-SA		
Blagojevic-Bucknall	2018	UK	Retro. cohort	CM	5.8	52.2 (1.2)	52.2 (12.2)	15,879	63,296	782	1651	1.42 (1.29–1.56)*	8
Zhang	2015	UK	Retro. cohort	CM	1	53 (12)	54 (12)	9865	43,598	76	194	1.50 (1.10–2.10)#	7
Yi-Fong Su	2014	Taiwan of China	Pros. cohort	CM	6.58	46.5 (14.5)	46.5 (14.5)	4365	17,452	212	899	0.94 (0.81–1.09)*	7
Roddy	2013	UK	Cross-sectional	LM	/	62.5 (15.3)	62.5 (15.4)	NA	NA	1689	6756	1.49 (0.70–3.14)$	5

Adjusted factors

Age, gender, BMI, alcohol, diabetes mellitus, ischemic heart disease, hypertension, hyperlipidemia, and use of diuretics drugs

Age, BMI, alcohol use, chronic renal disease, diabetes, hypertension, ischemic heart disease, use of aspirin, diuretics, losartan, and number of GP visits

Re-existing diabetes mellitus, hypertension, hyperlipidemia, heart failure, coronary artery disease, COPD, asthma, cerebrovascular disease, cancer, chronic kidney disease, alcoholism, and tuberculosis age, year of first gout consultation, gender, practice, type II diabetes mellitus, ischaemic heart disease, hypertension and diuretic prescription

SD, standard deviation; *OSAS*, obstructive sleep apnea syndrome; *HR*, hazard ratio; *CI*, confident interval; *hazard ratio; # risk ratio; $ odds ratio; *CM*, Cox regression model; *LM*, logistic regression model; *NA*, not available; *BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease

Subgroup analysis: AHI

AHI ≧ 30: the total WMD in the studies with average AHI ≧ 30 was more significant, with a corresponding value of 64.80 (95% CI 46.72–82.87, $p = 0.000$). AHI < 30: the total WMD in the studies with average AHI < 30 was significant, with a corresponding value of 19.82 (95% CI 11.34–28.31, $p = 0.176$). AHI not available: the total WMD in the studies with average AHI not available was significant, with a corresponding value of 63.13 (95% CI 34.07–92.20, $p = 0.000$) (Fig. 3).

Sensitivity analyses

Sensitivity analyses were performed to assess the influence of individual study on the pooled results by sequentially removing each eligible study. Results showed that removal of any study from the analysis did not subvert the present pooled analysis result (data not shown). Similar results revealed in the fixed effects model (WMD 35.33, 95% CI 31.35–39.31, $p = 0.000$).

Publication bias

The Begg tests ($p = 0.019$) and Egger tests ($p = 0.009$) provide evidence of publication bias in our study.

Meta-regression analysis

The univariate meta-regression analysis was conducted that the result variable was the WMD of serum uric acid levels, and publication year, average age, BMI, and AHI of OSAS patients were the covariates. Levels of serum uric acid were not significantly linked with following factors, including OSAS patients' age ($p = 0.993$), BMI ($p = 0.926$), and year of publication ($p = 0.473$). However, meta-regression indicated that the OSAS patients' AHI (an indicator of OSAS severity) might be the source of heterogeneity ($p = 0.001$).

Association between OSAS and gout

Four studies [51–54] examined the association between OSAS gout: three were cohort studies and one was a cross-sectional study. The three cohort studies (154,455 participants, a total of 3814 gouts were diagnosed) used the Cox proportional hazard model [51–53] and the cross-sectional study used logistic regression model [54]. Although in the cross-sectional study, Roddy et al. found that the prevalence of sleep apnea was higher among gout patients as compared with non-gout individuals [54]. Cross-sectional studies are difficult to determine the temporal relationship between cause and effect, and it has insufficient power to demonstrate an independent association between gout and OSAS. We only included three

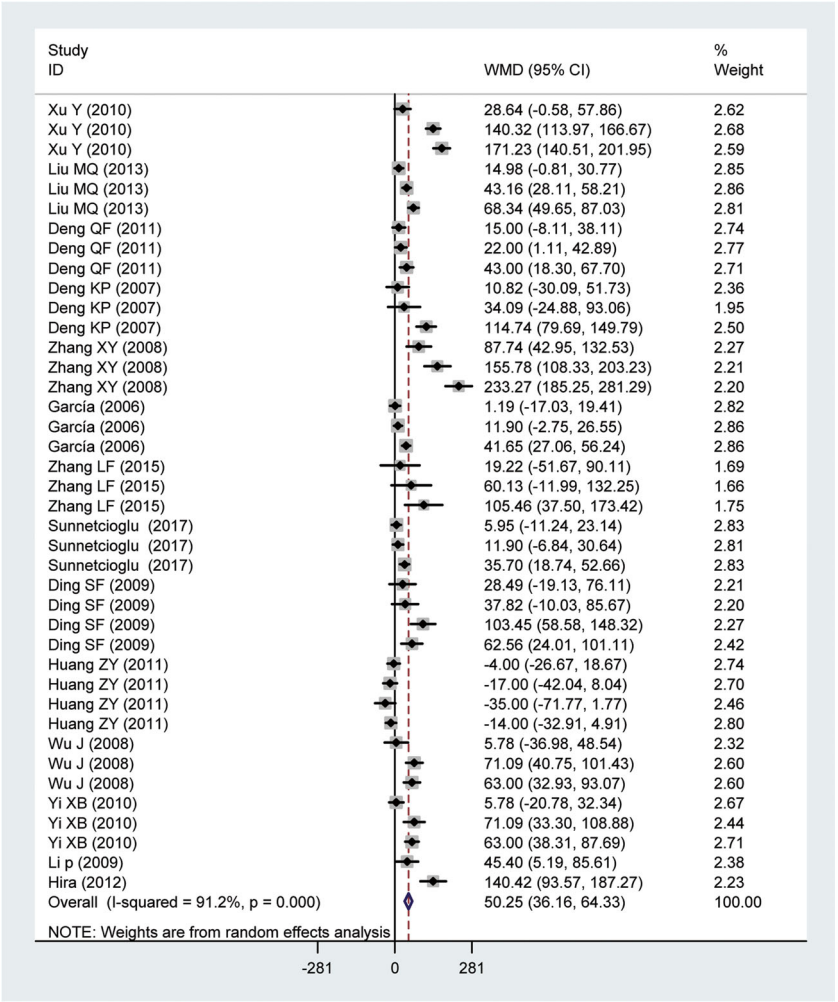

Fig. 2 Forest plot of the association between OSAS and serum uric acid levels

cohort studies in our analysis. A cohort study [52], undertaken in a UK primary care database, The Health Improvement Network (THIN), found that people with OSAS had 50% higher risk of developing gout over a 1-year follow-up period than those without OSAS, regardless of gender or obesity status. Blagojevic-Bucknall et al. assessed both the short- and long-term association between OSAS with gout in large primary care–based population. Results showed that increased risk persists beyond the first year after OSA diagnosis, with overall risk peaking 1 to 2 years after index date in patients with normal BMI as well as those who were overweight or obese [51]. However, a prospective cohort conducted by Yi-Fong Su et al. in Taiwan of China derived no significant results [53] (Table 2).

Because between-study heterogeneity was significant ($I^2 = 91.0\%$), the random-effects model was adopted. The pooled HR indicated a higher but not significant risk of developing gout in individuals suffering OSAS (HR 1.25, 95% CI 0.91–1.70). Because of the small number of included studies, it was difficult to assess the publication bias through visual assessments, and therefore, the funnel plot was not made. Both the p values of the Begg test ($p = 1.000$) and the Egger test ($p = 0.876$) are more than 0.05; therefore, publication bias may not exist. Furthermore, because only three studies included in our analysis, subgroup and sensitivity analysis were all not performed.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to examine the relationship between OSAS and serum uric acid level and gout. Our meta-analysis indicated that the serum uric acid levels were increased in patients with OSAS (WMD 50.25, 95% CI 36.16–64.33, $p < 0.01$), particularly in those patients with severe OSAS (WMD 82.87, 95% CI 53.00–112.74, $p < 0.01$). We also stratified the data into subgroups according to age (< 15 and ≧ 15), AHI (≧ 30 and < 30), and BMI (underweight, normal weight, overweight, and obesity). The results showed that the parameters had a more significant effect on serum uric acid levels when average age > 15, AHI ≧ 30, overweight, and obesity

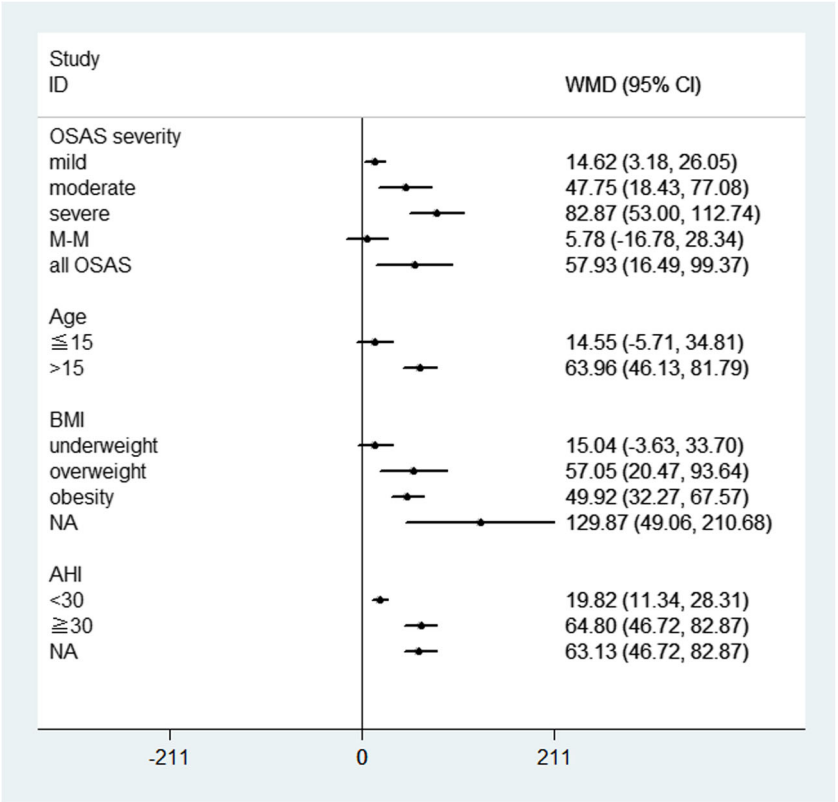

Fig. 3 Subgroup analyses: OSAS severity, age, BMI, AHI

OSAS patients. This tells us that patients with severe OSAS of a younger age are more susceptible to hyperuricemia, and more attention should be paid to young and severe OSAS patients. And our analysis showed a higher but not significant risk for OSAS patient to develop gout.

The possible biological mechanisms behind the association between OSAS and high serum uric acid level are as follows: first, the repeated episodes of upper airway obstruction that characterize OSAS produce decreases in arterial oxygen saturation repeatedly over the course of the night. Aerobic metabolism reduces and anaerobic glycolysis increases, which may accelerate the degradation of the energy substance adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and further metabolism to xanthine, increasing the source of purine in the body, leading to elevated blood uric acid (the end product of purine catabolism) levels. Second, due to long-term sleep disturbance, hypoxia causes a decrease in ATP production in tissue cells, and the inhibition of phosphoribosyl amide transferase is weakened, and an increase in purine production leads to an increase in blood uric acid levels. The main possible mechanisms for the development of high blood uric acid levels to promote cardiovascular disease are as follows: first, oxidative metabolism, xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and eventually forms uric acid, which produces metabolites such as NO and reactive oxygen species (ROS). NO has the function of relaxing blood vessels. Uric acid can reduce the activity of NO [55], affecting the diastolic function of blood vessels, leading to excessive vascular tone. Second, endothelial dysfunction [56], one of the important products of purine metabolism, ROS, due to its ultra-high activity, accumulation in the body may damage the normal metabolism of DNA, ribonucleotide (RNA), protein, fat, and glucose; affect its normal physiological functions, causing DNA breaks, abnormal DNA damage repair mechanisms, and lipid peroxidation, leading to vascular endothelial cell damage and normal physiological dysfunction of vascular endothelial cells; easily lead to vascular endothelial lipid deposition caused by atherosclerosis and other diseases; and promote the occurrence and development of cardiovascular and cerebrovascular diseases. At the same time, urate crystals can also be deposited on the blood vessel wall, directly affecting the function of vascular endothelial cells and destroying vascular endothelial cells. Third, platelet adhesion and aggregation: blood uric acid activates platelets, promotes platelet adhesion and aggregation, and leads to thrombosis. In addition, hyperuric acid concentration promotes lipid peroxidation and accelerates the progression of atherosclerosis. The main possible mechanisms of OSAS leading to cardiovascular disease are as follows: oxidative stress [57, 58], sympathetic excitation abnormalities [59], inflammatory response [60], renin-angiotensin-aldosterone system (RAAS) activate [59]. Therefore, both OSAS and hyperuricemia can increase the incidence and mortality of cardiovascular disease. There is a similar pathophysiological mechanism between them.

Therefore, elevated serum uric acid levels in OSAS patients may further lead to an increase in gout and cardiovascular disease morbidity and mortality.

Despite the meaningful findings, our study was not without limitations. Firstly, studies included in the meta-analysis of the association between OSAS and serum uric acid level were either case-control or cross-sectional trails, each, possibly, having a degree of experimental bias. Secondly, the number of included studies for the association between OSAS and gout were small. More studies with larger sample size would be needed. Thirdly, previous studies have shown that CPAP can reduce the uric acid level of OSAS patients to normal values [61], but most of the studies we included did not provide information on whether the subjects were treated, which made us unable to perform subgroup analysis according to whether or not CPAP treatment was received. Therefore, our study could not provide evidence for CPAP to reduce uric acid levels in OSAS patients. Finally, high heterogeneity was present among individual studies, but except AHI of OSAS patients, we failed to find other exact sources of heterogeneity from the limited studies included.

Conclusion

Our analysis suggested that serum uric acid levels in OSAS patients were 50.25 μmmol/L higher than controls, the association between OSAS and gout did not reach statistical significance (but there was a trend). And the previous meta-analysis demonstrated that hyperuricemia is an independent risk factor for cardiovascular disease [28, 29]. As the hypoxia-associated hyperuricemia among OSAS patients is treatable, studying the changes of serum uric acid level in patients with OSAS and clarifying the role of OSAS on the risk of incident gout are of great significance for the prevention and control of gout and cardiovascular disease. However, whether or not OSAS patients are susceptible to gout warrant further study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human and animals participants performed by any of the authors.

References

1. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, Nuki G (2008) Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 67(7):960–966. https://doi.org/10.1136/ard.2007.076232
2. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG (2005) Gout epidemiology: results from the UK general practice research database, 1990-1999. Ann Rheum Dis 64(2):267–272. https://doi.org/10.1136/ard.2004.024091
3. Zhu Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 63(10):3136–3141. https://doi.org/10.1002/art.30520
4. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M (2015) Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 74(4):661–667. https://doi.org/10.1136/annrheumdis-2013-204463
5. Klemp P, Stansfield SA, Castle B, Robertson MC (1997) Gout is on the increase in New Zealand. Ann Rheum Dis 56(1):22–26. https://doi.org/10.1136/ard.56.1.22
6. Cassim B, Mody GM, Deenadayalu VK, Hammond MG (1994) Gout in black South Africans: a clinical and genetic study. Ann Rheum Ddis 53(11):759–762. https://doi.org/10.1136/ard.53.11.759
7. Zeng Q, Wang Q, Chen R, Xiao Z, Huang S, Xu J (2003) Primary gout in Shantou: a clinical and epidemiological study. Chinese Medical J 116(6):66–69
8. Roddy E, Choi HK (2014) Epidemiology of gout. Rheum Dis Clin N Am 40(2):155–175. https://doi.org/10.1016/j.rdc.2014.01.001
9. McAdams-DeMarco MA, Maynard JW, Baer AN, Coresh J (2012) Hypertension and the risk of incident gout in a population-based study: the atherosclerosis risk in communities cohort. J Clin Hypertens 14(10):675–679. https://doi.org/10.1111/j.1751-7176.2012.00674.x
10. Maynard JW, McAdams-DeMarco MA, Baer AN, Köttgen A, Folsom AR, Coresh J, Gelber AC (2012) Incident gout in women and association with obesity in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Med 125(7):717.e9717. https://doi.org/10.1016/j.amjmed.2011.11.018
11. Choi HK, Ford ES, Li C, Curhan G (2007) Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 57(1):109–115. https://doi.org/10.1002/art.22466
12. Zhu Y, Pandya BJ, Choi HK (2012) Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 125(7):679–687.e1. https://doi.org/10.1016/j.amjmed.2011.09.033
13. Richette P, Clerson P, Bouee S et al (2015) Identification of patients with gout: elaboration of a questionnaire for epidemiological studies. Ann Rheum Dis 74(9):1684–1690. https://doi.org/10.1136/annrheumdis-2013-204976
14. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH, Research MRFIT (2008) Group: long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med 168(10):1104–1110. https://doi.org/10.1001/archinte.168.10.1104
15. Kuo CF, See LC, Luo SF, Ko YS, Lin YS, Hwang JS, Lin CM, Chen HW, Yu KH (2010) Gout: an independent risk factor for all-cause and cardiovascular mortality. Rheumatology 49(1):141–146. https://doi.org/10.1093/rheumatology/kep364
16. Listed NA (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 22(5):662–689
17. Lindberg E, Gislason T (2000) Epidemiology of sleep-related obstructive breathing. Sleep Med Rev 4(5):411–433. https://doi.org/10.1053/smrv.2000.0118
18. Sasanabe R, Banno K, Otake K et al (2006) Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 29(5):315–322. https://doi.org/10.1291/hypres.29.315

19. Parish JM, Adam T, Facchiano L (2007) Relationship of metabolic syndrome and obstructive sleep apnea. J Clin Sleep Med 3(5):467–472
20. Kono M, Tatsumi K, Saibara T, Nakamura A, Tanabe N, Takiguchi Y, Kuriyama T (2007) Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. Chest 131: 1387–1392. https://doi.org/10.1378/chest.06-1807
21. Chou YT, Chuang LP, Li HY et al (2010) Hyperlipidaemia in patients with sleep-related breathing disorders: prevalence & risk factors. Indian J Med Res 131(5):121–125. https://doi.org/10.1378/chest.06-1807
22. West SD, Nicoll DJ, Stradling JR (2006) Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 61(11):945–950. https://doi.org/10.1136/thx.2005.057745
23. Shahar E, Whitney CW, Redline S et al (2001) Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 163(1):19–25. https://doi.org/10.1164/ajrccm.163.1.2001008
24. Choi HK, Atkinson K, Karlson EW, Curhan G (2005) Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 165(7):742–748. https://doi.org/10.1001/archinte.165.7.742
25. Ruiz Garcia A, Sanchez Armengol A et al (2006) Blood uric acid levels in patients with sleep-disordered breathing. Arch Bronconeumol 42(10):492–500. https://doi.org/10.1016/S1579-2129(06)60575-2
26. Plywaczewski R, Bednarek M, Jonczak L, Gorecka D, Sliwiniski P (2005) Hyperuricaemia in males with obstructive sleep apnoea (OSA). Pneumonol Alergol Pol 73(3):254–259
27. Plywaczewski R, Bednarek M, Jonczak L, Gorecka D, Sliwinski P (2006) Hyperuricaemia in females with obstructive sleep apnoea. Pneumonol Alergol Pol 74(4):159–165
28. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA (2010) Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res 62(2):170–180. https://doi.org/10.1002/acr.20065
29. Krishnan E, Pandya BJ, Chung L, Dabbous O (2011) Hyperuricemia and the risk for subclinical coronary atherosclerosis–data from a prospective observational cohort study. Arthritis Res Ther 13(2):R66. https://doi.org/10.1186/ar3322
30. Choi HK, Niu J, Neogi T, Chen CA, Chaisson C, Hunter D, Zhang Y (2015) Nocturnal risk of gout attacks. Arthritis Rheumatol 67(2): 555–562. https://doi.org/10.1002/art.38917
31. Mirrakhimov AE, Mirrakhimov EM (2013) Obstructive sleep apnoea, gout and cardiovascular risk: a worth studying association. Med Hypotheses 81(4):749. https://doi.org/10.1016/j.mehy.2013.07.042
32. Abrams B (2012) High prevalence of gout with sleep apnea. Med Hypotheses 78(2):349. https://doi.org/10.1016/j.mehy.2011.10.029
33. Abrams B (2009) Sleep apnea as a cause of gout flares. Medscape J Med 11:3
34. Simkin PA (2009) The pathogenesis of podagra. Medscape J Med 11(1):3
35. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005
36. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22(4): 719–748. https://doi.org/10.1093/jnci/22.4.719
37. He W, Li Q, Yang M, Jiao J, Ma X, Zhou Y, Song A, Heymsfield SB, Zhang S, Zhu S (2015) Lower BMI cutoffs to define overweight and obesity in China. Obesity 23(3):684–691. https://doi.org/10.1002/oby.20995
38. Li P, Yan L, Su L, Li Q (2009) Changes of uric acid and blood lipids in patients with obstructive sleep apnea hypopnea syndrome complicated with coronary heart disease. Shandong Medical Journal 49(29):33–34. https://doi.org/10.3969/j.issn.1002-266X.2009.29.014
39. Xu H, Cao F, Wei GR et al (2010) Association between the condition and plasma uric acid levels and carotid atherosclerosis in patients with obstructive sleep apnea hypopnea syndrome. Journal of Clinical Neurology 23(06):411–413
40. Liu MQ, Bi JY, Wan JM (2013) Changes of blood uric acid before and after operation in children with obstructive sleep apnea hypopnea syndrome. Medical Journal of Wuhan University 34(05):733–736. https://doi.org/10.14188/j.1671-8852.2013.05.041
41. Deng QF (2011) Changes of blood uric acid and lipids in children with obstructive sleep apnea hyperpnoea. Chinese General Practice 14(34):3943–3945. https://doi.org/10.3969/j.issn.1007-9572.2011.34.019
42. Deng KP, Zhang LJ, Yang C (2007) Changes of indirect bilirubin and uric acid levels in patients with obstructive sleep apnea hypopnea syndrome. Chinese Journal of Microcirculation 17(02): 35–36. https://doi.org/10.3969/j.issn.1005-1740.2007.02.014
43. Ding SF, Wang L, Liu Y, Liu HY, Xie F (2009) The relationship between obstructive sleep apnea-hypopnea syndrome and blood uric acid levels. Journal of Cardiovascular and Pulmonary Diseases 28(06):400–403. https://doi.org/10.3969/j.issn.1007-5062.2009.06.008
44. Wu J, Liu YH (2008) Clinical study on serum uric acid and bilirubin levels in patients with obstructive sleep apnea hypopnea syndrome. Acta Universitatis Medicinalis Anhui 43(06):706–708. https://doi.org/10.3969/j.issn.1000-1492.2008.06.030
45. Zhang XY, Ye XW, Feng RX, Rao SS (2008) The study between serum uric acid and early morning blood pressure of obstructive sleep apnea syndrome patients. Chinese Journal of Practical Internal Medicine 28(S1):94–95
46. Yi XB (2010) Obstructive sleep apnea-syndrome in patients with serum uric acid and lipid levels of correlation. China Modern Medicine 17(04):11–13. https://doi.org/10.3969/j.issn.1674-4721.2010.04.007
47. Huang ZY, Liu DB, Wan GP, Zhong JW, Tan ZY, Wei W, Xu JJ, Shao JB, Qiu SY (2011) Correlation between serum uric acid levels and obstructive sleep apnea/hypopnea syndrome in children. Chinese Journal of Pediatrics 49(3):218–220. https://doi.org/10.3760/cma.j.issn.0578-1310.2011.03.014
48. Zhang LF (2015) Association between obstructive sleep apnea hypopnea syndrome and uric acid in male [D]. Fujian University of Medicine CNKI:CDMD:2.1015.991504
49. Sunnetcioglu A, Gunbatar H, Yıldız H (2018) Red cell distribution width and uric acid in patients with obstructive sleep apnea. Clin Respir J 12(3):1046–1052. https://doi.org/10.1111/crj.12626
50. Hira HS, Shukla A, Kaur A, Kapoor S (2012) Serum uric acid and lactate levels among patients with obstructive sleep apnea syndrome: which is a better marker of hypoxemia? Ann Saudi Med 32(1):37–42. https://doi.org/10.5144/0256-4947.2012.37
51. Blagojevic-Bucknall M, Mallen C, Muller S, Hayward R, West S, Choi H, Roddy E (2018) The risk of gout among patients with sleep apnea: a matched cohort study. Arthritis Rheumatol 71(1):154–160. https://doi.org/10.1002/art.40662
52. Zhang Y, Peloquin CE, Dubreuil M, Roddy E, Lu N, Neogi T, Choi HK (2015) Sleep apnea and the risk of incident gout: a population-based, body mass index-matched cohort study. Arthritis Rheumatol 67(12):3298–3302. https://doi.org/10.1002/art.39330
53. Yi-Fong Su Y, Hong JY, Perng DW (2014) Obstructive sleep apnea and risk of gout-a nationwide population-based study. Thorac Med 29(5):272–279
54. Roddy E, Muller S, Hayward R, Mallen CD (2013) The association of gout with sleep disorders: a cross-sectional study in primary care.

BMC Musculoskeletal Dis 14(119). https://doi.org/10.1186/1471-2474-14-119

55. Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN (2008) Inactivation of nitric oxide by uric acid. Nucleosides Nucleotides Nucleic Acids 27(8):967–978. https://doi.org/10.1080/15257770802257952
56. Ho WJ, Tsai WP, Yu KH, Tsay PK, Wang CL, Hsu TS, Kuo CT (2010) Association between endothelial dysfunction and hyperuricaemia. Rheumatology 49(10):1929–1934. https://doi.org/10.1093/rheumatology/keq184
57. Yamauchi M, Kimura H (2008) Oxidative stress in obstructive sleep apnea: putative pathways to the cardiovascular complications. Antioxid Redox Signal 10(4):755–768. https://doi.org/10.1089/ars.2007.1946
58. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH (2008) Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 117(17):2270–2278. https://doi.org/10.1161/CIRCULATIONAHA.107.741512
59. Prabhakar NR, Kumar GK (2010) Mechanisms of sympathetic activation and blood pressure elevation by intermittent hypoxia. Respir Physiol Neurobiol 174(1–2):156–161. https://doi.org/10.1016/j.resp.2010.08.021
60. Pant S, Deshmukh A, Gurumurthy GS, Pothineni NV, Watts TE, Romeo F, Mehta JL (2014) Inflammation and atherosclerosis–revisited. J Cardiovasc Pharmacol Ther 19(2):170–178. https://doi.org/10.1177/1074248413504994
61. Sahebjani H (1998) Changes in urinary uric acid excretion in obstructive sleep apnea before and after therapy with nasal continuous positive airway pressure. Chest 113(6):1604–1608. https://doi.org/10.1378/chest.113.6.1604