Serum Uric Acid and the Risk of Incident and Recurrent Gout: A Systematic Review

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ABSTRACT. ***Objective.*** Lowering serum uric acid (SUA) levels can essentially cure gout; however, this is not widely practiced. To summarize epidemiologic evidence related to this causal link, we conducted a systematic review of the published literature reporting the association between SUA level and incident and recurrent gout (i.e., gout flares).

Methods. We systematically searched Medline, EMBASE, and the Cochrane Database of Systematic Reviews using separate search strategies for incident gout and recurrent gout. We screened 646 abstracts to identify 8 eligible articles reporting gout incidence and 913 abstracts to identify 18 articles reporting recurrent gout.

Results. For both gout incidence and recurrence, a graded trend was observed where the risk was increased with higher SUA levels. Gout incidence rates per 1000 person-years from population-based studies ranged from 0.8 (SUA ≤ 6 mg/dl) to 70.2 cases (SUA ≥ 10 mg/dl). Recurrent gout risk in clinical cohorts ranged from 12% (SUA ≤ 6 mg/dl) to 61% (SUA ≥ 9 mg/dl) among those receiving urate-lowering therapy (ULT), and 3.7% (SUA 6–7 mg/dl) to 61% (SUA > 9.3 mg/dl) after successful ULT. Retrospective database studies also showed a graded relationship, although the strength of the association was weaker. Studies reporting mean flares or time-to-flare according to SUA showed similar findings.

Conclusion. This systematic review confirms that higher SUA levels are associated with increased risk of incident and recurrent gout in a graded manner. Although few prospective cohorts have evaluated incident and recurrent gout according to SUA, the existing evidence underscores the need to treat to SUA targets, as recommended by the American College of Rheumatology and the European League Against Rheumatism. (J Rheumatol First Release February 1 2017; doi:10.3899/jrheum.160452)

Key Indexing Terms:
GOUT URIC ACID HYPERURICEMIA

Gout is one of the most common inflammatory arthritic diseases[1], with an estimated prevalence of about 4% among adults in the United States[2]. It is characterized by the formation of monosodium urate (MSU) crystals in the synovial fluid of the joints, as well as in other tissues[3]. The most common symptom is sudden and severe pain in the joint along with swelling and redness, with the first metatarsophalangeal joint of the big toe being the most frequently affected. The clinical burden among individuals with gout is not limited to rheumatologic disease; however, those with gout have a greater likelihood of developing diabetes mellitus[4] and cardiovascular disease, and are at increased risk of all-cause death compared with those without gout[5]. Appropriate management of the symptoms of gout is important, not only because of the high patient burden and negative effect of gout on health-related quality of life, but also to reduce the risk of irreversible joint damage, chronic pain and disability, other serious chronic conditions, and premature death[6].

Hyperuricemia is a key causal factor for gout[7], and all patients with gout are expected to experience at least some periods of hyperuricemia[7,8,9,10,11]. Treatment targets for gout in clinical practice as well as clinical trials have focused on lowering serum uric acid (SUA) to the subsaturation range, (e.g., < 6.0 mg/dl or < 5.0 mg/dl)[12,13,14]. Because supersaturation and crystallization of MSU occur when the urate level is about 6.8 mg/dl or higher, reducing SUA levels to below this threshold ensures that MSU crystals can dissolve, which serves to prevent acute gout flares, remove tophi, and improve longterm prognoses[14,15].

Despite this causal relation between hyperuricemia and gout[13,16,17], and the expected curing of gout by effective urate reduction[1,11,14], this is not widely accepted and practiced. To summarize epidemiologic evidence related to this causal link,

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we conducted a systematic review of the published literature reporting (1) the association between prior SUA levels and the risk of incident gout among gout-free individuals, and (2) the frequency or risk of recurrent gout (or gout flares) according to SUA level among individuals with preexisting gout.

MATERIALS AND METHODS

The systematic literature review was undertaken in July 2015 using 2 search strategies conducted in Medline, EMBASE, and the Cochrane Database of Systematic Reviews to identify relevant citations published and indexed prior to this date. Conference abstracts were considered for inclusion if they were dated within 2 years of the search (i.e., July 2013 to July 2015). The first search strategy aimed to identify any observational studies that estimated the risk of incident gout according to SUA level among gout-free individuals, while the second search strategy aimed to identify any observational studies or randomized trials that reported the risk of recurrent gout according to SUA level among those with preexisting gout. Our inclusion criteria (according to the Population, Intervention, Comparisons, Outcomes, and Study Design) are described in Table 1. No limitations on language were specified for the search.

The search strategy included terms related to gout, incidence, SUA, and observational studies (for the incident gout search strategy), and recurrent gout, flares, and SUA (for the recurrent gout search strategy). Two investigators independently reviewed all abstracts identified by the search strategy against the inclusion criteria. Article eligibility was decided by consensus, and if discrepancies occurred between the studies selected by the 2 reviewers, a third reviewer provided arbitration.

Similarly, data extraction was performed by 2 investigators to obtain data on study and patient characteristics, and reported outcomes. Any discrepancies observed between the data identified by the 2 reviewers were resolved by consensus. Study characteristics extracted consisted of features of design, inclusion and exclusion criteria, sample size, study location(s), and periods over which the risk of incident or recurrent gout were ascertained. Patient characteristics included the mean age and sex distribution, comorbidities, risk factors for gout, and family history. The quality of the studies included was assessed by the Strengthening of Reporting of Observational Studies in Epidemiology checklist[18].

Data on incident gout were extracted, including the proportion developing gout, the rate of gout per person-year, and the relative risk (RR), hazard ratio (HR), or incidence rate ratio (IRR) of developing gout. Data on SUA level were extracted as either the proportion of the sample within a given SUA level category or as the mean SUA for the sample or subgroup. Data on the risk of recurrent gout included the number and proportion of those developing recurrent gout flares and the mean number of flares.

These data were summarized in tabular form or synthesized graphically. Estimates were stratified by study design (prospective vs retrospective) and timing of SUA assessment [prior to flare assessment (prospective assessment of flares) or after flare assessment (retrospective assessment of flares)] for the risk of recurrent gout.

For the risk of incident gout, IRR were calculated if that measure was not presented in the original article. To do so, the incidence rate observed among those with gout at higher SUA levels was divided by the incidence rate of the referent category (i.e., the lowest SUA category). For recurrent gout, risk ratios were calculated to compare the proportion of those with gout experiencing flares according to SUA category.

RESULTS

We screened 646 abstracts to identify 8 eligible articles describing incident gout, and 913 abstracts to identify 17 studies (described in 18 articles) describing recurrent gout (Figure 1A and Figure 1B). The list of included studies for both searches are provided in Supplementary Table 1A and Supplementary Table 1B (available with the online version of this article). The quality of reporting was generally high, although 7 studies provided few details on potential sources of bias[19,20,21,22,23,24,25] and 4 studies were unclear on the funding source or role of the funders of the study[21,23,26,27].

SUA and incident gout. Of the 8 studies identified focusing on incident gout, 5 (62.5%) presented estimates according to SUA category[7,16,28,29,30]. Of the 5 studies, 3 prospectively evaluated the incidence of gout from population-based samples while 2 were non-population–based studies. For the risk of incident gout, a graded trend was observed where the risk of gout increased with higher SUA levels.

From the 3 prospective population-based studies[16,29,30], incidence rates of gout per 1000 person-years ranged from 0.8 new cases at the lowest SUA level (< 6 mg/dl) to 70.2 new cases at SUA level ≥ 10 mg/dl (Table 2). IRR, reflecting the increased risk of developing gout for patients in each SUA category compared with the lowest SUA category, were also higher with higher SUA levels (Figure 2). Because the Normative Aging Study included only men, IRR (95% CI) among men in the study ranged from 1.1 (0.3–2.0 for SUA of 6.0–6.9 mg/dl) to 87.8 (86.8–88.7 for SUA ≥ 10.0 mg/dl)[29]. Sex-specific IRR were also available from the Framingham Heart Study, and ranged from 2.4 (1.5–4.0) for

Table 1. Inclusion criteria according to PICOS for the risk of incident gout and recurrent gout.

Variables	Risk of Incident Gout	Risk of Recurrent Gout
Population	Gout-free individuals with available SUA data	Individuals with preexisting gout
Interventions/comparisons	SUA levels at baseline	SUA levels at baseline stratified by urate-lowering therapy use
Outcomes	Incident gout	Recurrent gout
Study design	Observational studies including prospective cohort studies/registries and retrospective cohort studies/database studies	Observational studies including prospective cohort studies/registries and retrospective cohort studies/database studies and randomized trials

PICOS: Population, Intervention, Comparisons, Outcomes, and Study Design; SUA: serum uric acid.

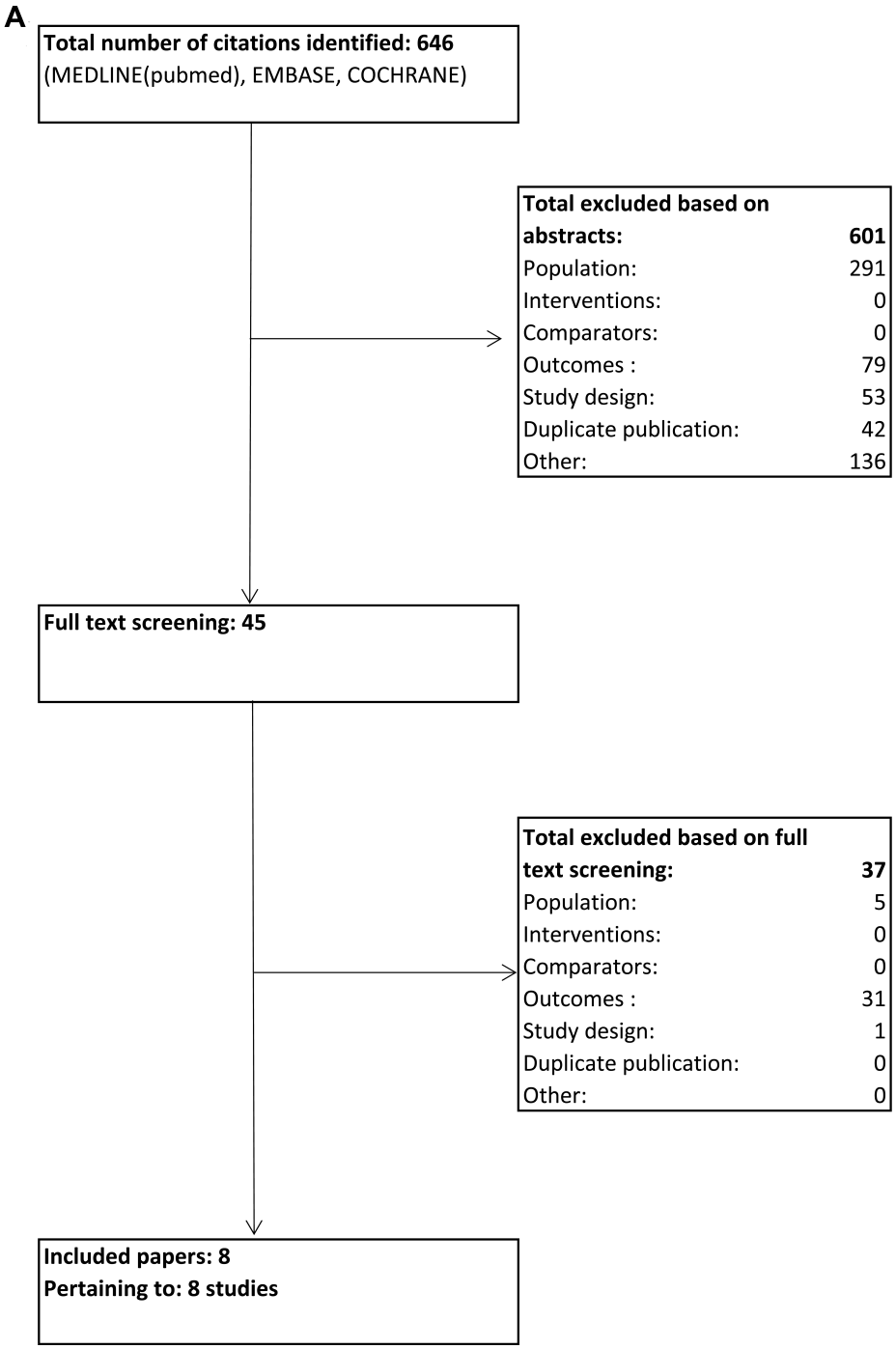


Figure 1. Flow diagram for study inclusion for (A) incident gout and (B) recurrent gout.

women with SUA of 5.0–5.9 mg/dl, up to 47.9 (24.0–95.5) for men with SUA ≥ 8.0 mg/dl[16].

IRR for the 2 remaining studies, 1 prospective[28] and 1 retrospective[7], that also measured incident gout according to SUA categories are also presented in Figure 2. Ascertainment of SUA status was incomplete in the retrospective database study, where SUA levels were recorded on 2021 individuals (65.9%) with gout and 3103 non-gout individuals (33.7%)[7]. Although exact categories of SUA varied between studies, findings consistently showed a higher risk of incident gout among those with higher SUA levels.

Seven of the 9 studies (77.8%) reported the mean SUA levels according to the development of incident gout during the followup (Supplementary Table 2, available with the

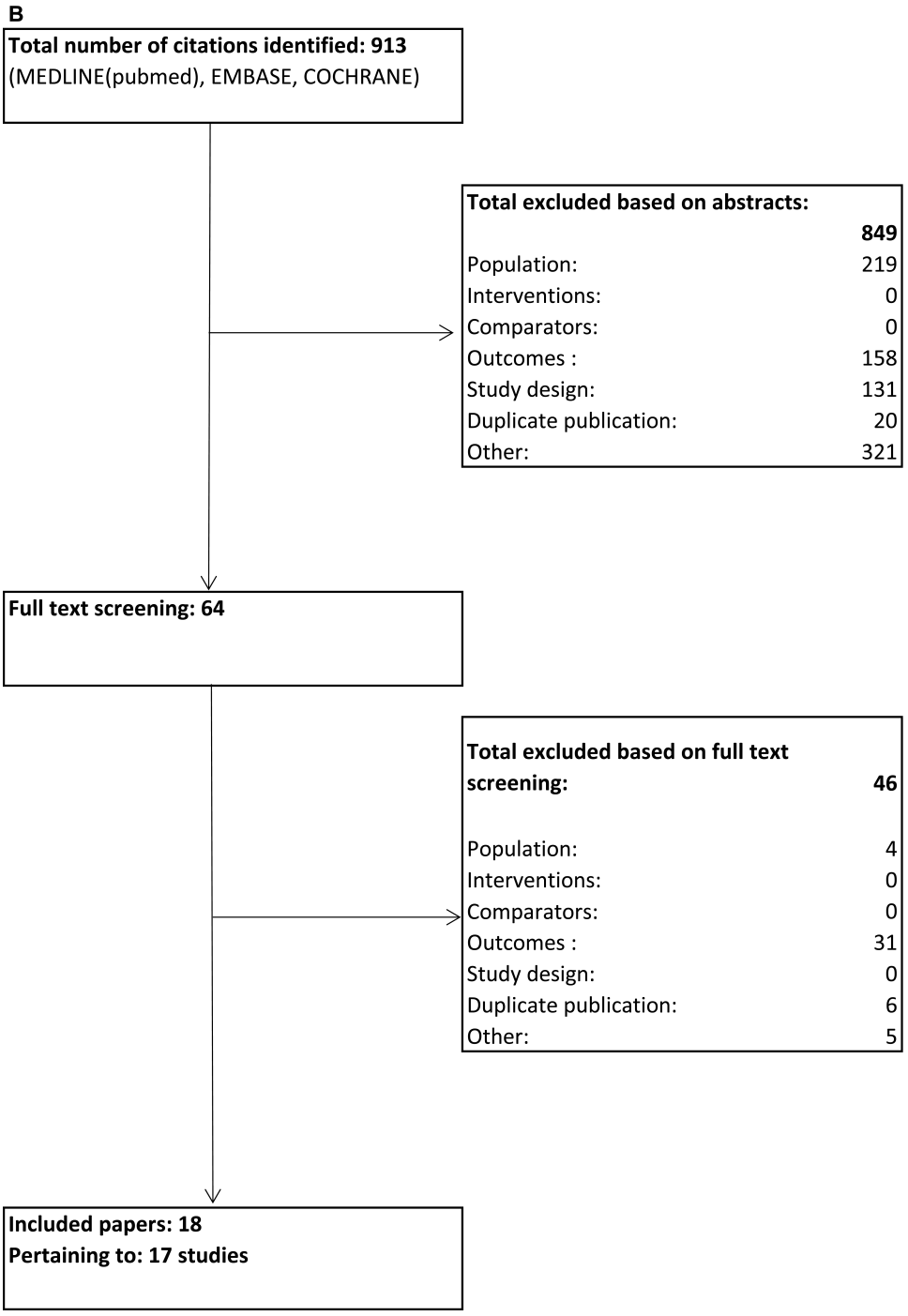


Figure 1. Continued.

online version of this article)[16,28,29,30,31,32,33]. Mean SUA levels among gout-free individuals ranged from 5.0 ± 1.1 mg/dl among women ≤ 50 years of age[31] to 6.8 mg/dl among men[28]. Mean estimates among those who developed incident gout ranged from 6.1 ± 1.7 mg/dl among women ≤ 50 years of age[31] to 8.8 ± 1.8 mg/dl among individuals with rheumatologist-managed gout[30]. When mean SUA levels were compared between those who developed gout and those who remained gout-free, mean SUA was up to 1.6-fold higher among those who developed gout.

SUA and recurrent gout. Of the 18 studies identified reporting on recurrent gout, 7 presented data on the proportion of the sample experiencing flares according to SUA categories[19,21,22,23,34,35,36] and 10 studies (in 11 articles)

Table 2. The risk of incident gout according to SUA category, overall and by sex, from prospective population-based studies.

Study	Followup, Yrs	SUA Category, mg/dl	Overall			Males			Females		
			Cases, n	IR	IRR (95% CI)	Cases, n	IR	IRR (95% CI)	Cases, n	IR	IRR (95% CI)
Campion, *et al*[29,a,*]	14.9	≤ 6				10	0.8	Referent	—	—	—
		6.0–6.9				13	0.9	1.1 (0.3–2.0)	—	—	—
		7.0–7.9				21	4.1	5.1 (4.4–5.9)	—	—	—
		8.0–8.9				14	8.4	10.5 (9.7–11.3)	—	—	—
		9.0–9.9				18	43.2	54.0 (53.2–54.8)	—	—	—
		≥ 10.0				8	70.2	87.8 (86.8–88.7)	—	—	—
Bhole, *et al*[16,b]	28	< 5	63	0.8	—	17	0.8	Referent	46	0.8	Referent
		5–5.9	81	3.0	—	56	3.4	4.1 (2.4–7.1)	25	2.5	2.4 (1.5–4.0)
		6–6.9	78	6.1	—	64	8	9.5 (5.5–16.6)	14	4.2	3.4 (1.8–6.6)
		7–7.9	54	15.5	—	42	17.8	22.4 (12.3–40.6)	12	13.1	12.2 (5.9–25.3)
		≥ 8	28	30.1	—	21	32.9	47.9 (24.0–95.5)	7	27.3	22.5 (9.1–55.6)
Chen, *et al*[30,*]	7.3	< 6	—	1.5	—	—	2.3	Referent	—	0.7	Referent
		6–9	—	5.7	—	—	7.4	3.2 (NR)	—	4.1	6.1 (NR)
		> 9	—	28.7	—	—	38.4	16.5 (NR)	—	19.0	28.7 (NR)

[a] Most recent SUA was presented; SUA was measured every 5 years. [b] Authors presented adjusted HR of developing gout rather than IRR. * Crude rate ratio was calculated based on presented data. For Chen, *et al*[30], 95% CI were not calculated because SUA category-specific n were unknown. SUA: serum uric acid; IR: incidence rate (per 1000 person-yrs); IRR: incidence rate ratio; NR: not reported.

presented data on mean flares according to mean SUA level[19,20,24,25,26,27,37,38,39,40,41]. Similar to studies for incident gout, a graded trend was observed where the risk of recurrent gout increased with higher SUA levels.

Flares according to SUA category. Of the 7 studies presenting data on flares according to SUA category, 5 measured SUA prior to assessing flares (Table 3)[22,23,34,35,36]. Two of those were prospective clinical cohort studies that required clinical confirmation of flare status[22,23] and 3 were retrospective cohorts where gout flares were based on administrative data without clinical confirmation[34,35,36]. A graded relationship was observed where the proportion of patients experiencing flares was higher among those with higher SUA levels. The risk of recurrent gout in clinical cohorts ranged from 12% at SUA level ≤ 6 mg/dl to 61% at SUA level ≥ 9 mg/dl among those receiving urate-lowering therapy (ULT), whereas it ranged from 3.7% at SUA level > 6 mg/dl to < 7 mg/dl to 61% at SUA level > 9.3 mg/dl after successful ULT therapy[22,23].

Estimates from the retrospective cohorts without clinical confirmation of gout flares also showed a graded relationship (Table 3), although the magnitude of the association was smaller and the periods over which flares were assessed varied (from 1 to 5 yrs of followup). The proportions of patients experiencing flares in the lowest SUA category (< 6 mg/dl) varied from 23% over 5 years of followup to 46% over 2 years of followup[34,35,36]. Two of the retrospective studies also presented estimates of the mean number of flares per patient, which were also higher among those with higher SUA levels.

Risk ratios comparing the percentage of patients with recurrent gout according to SUA category were calculated; all comparisons showed a significantly increased risk with higher SUA levels (Table 3). Estimates from the 2 prospective studies suggest about a 4- to 9-fold increased risk of recurrent gout for patients with SUA in the 6 mg/dl or 7 mg/dl to 9 mg/dl range, and a 7.5- to 16.5-fold increased risk for patients with SUA > 9 mg/dl[22,23]. Findings from the retrospective studies also demonstrated increasing risk with higher SUA levels, although the magnitude of the risk increases was less, because of the higher proportions of patients with recurrent gout in the lower SUA categories (Table 3).

Two of the 7 studies presenting data on the risk of recurrent gout according to SUA category reported on flare frequency according to whether target SUA levels were achieved over the same period. The risk of recurrent gout was also higher among those with higher SUA levels. In 1 of these studies, a mean of 1.2 flares was observed over a 3-month period among those with SUA < 6.0 mg/dl, compared with 3.2 flares among those with SUA ≥ 6 mg/dl[19]. In the other, a mean of 1.0 flare was observed over a 12-month period among those with SUA ≤ 6.0 mg/dl, compared with 6.0 flares among those with SUA > 6 mg/dl[21].

Flares according to mean SUA. Among the 10 studies presenting mean flares per patient according to mean SUA level, time periods and study designs varied. Nonetheless, a graded relationship was also observed, where the mean number of flares was higher among those with higher SUA levels (Figure 3). Average estimates ranged from 2 flares per year per patient at a mean SUA level of 6.4 mg/dl to 4.6 flares per year per patient at a mean SUA level of 9.0 mg/dl[26,39].

DISCUSSION

We aimed to systematically review the literature to date

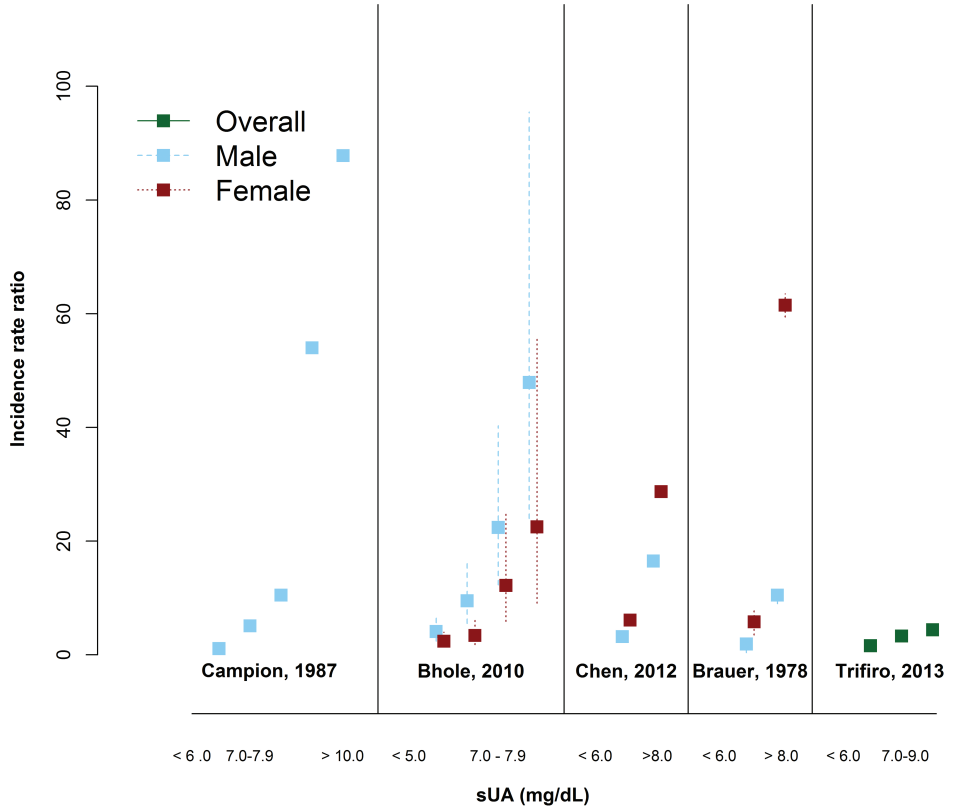
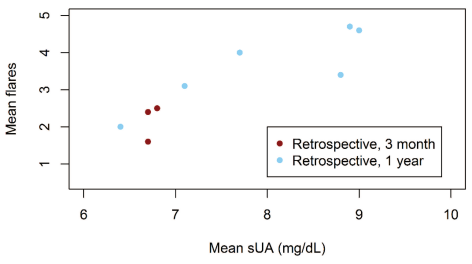


Figure 2. The increased risk of incident gout by IRR with 95% CI according to SUA category. Bhole, *et al*[16] presented HR rather than IRR. CI for Trifirò, *el al*[7] are presented in the plot, but are smaller than the box size (i.e., they are entirely contained within the box). Sample size data by which to calculate CI for Chen, *et al*[30] were unavailable. IRR: incidence rate ratio; SUA: serum uric acid.



Study	Flares		SUA Level, mg/dl	
	Mean (Median)	SD (Range)	Mean	SD
Retrospective (3 month) assessment of flares				
Dalbeth, *et al*[19]	2.5	—	6.8	—
Dalbeth, *et al*[38]	1.6	—	6.7	—
Chan, *et al*[37]	2.4	9.4	6.7	—
Retrospective (1 year) assessment of flares				
Mercieca, *et al*[26]	(2.0)	(0–9)	6.4	—
Khanna, *et al*[20]	4.6	3.6	9	1.3
Khanna, *et al*[39]	4.7	4.5	8.9	1.4
Singh, *et al*[27]	3.1	—	7.1	—
Rees, *et al*[41]	4.0	4	7.7	1.6
Perez-Ruiz, *et al*[40]	3.4	2.8	8.8	1.4

Figure 3. Mean (SD) flares according to mean (SD) SUA level stratified by timing of flare assessment. One randomized trial that described outcomes over 6 months among patients undergoing active treatment to lower SUA reported 3.4 mean flares among the sample with a mean SUA of 9.8 mg/dl at baseline[24,25]. SUA: serum uric acid.

reporting on the association between SUA and both incident gout and recurrent gout flares. Our findings confirm that higher SUA levels are associated with an increased risk of incident and recurrent gout in a graded manner, corroborating the key role of urate lowering in gout care. Nevertheless, there is a notable lack of understanding among many healthcare providers as to the true value of lowering SUA, and thus gout remains both underdiagnosed and undertreated despite the availability of effective SUA-lowering therapy[14,42]. However, data from our systematic review underscore the need to treat to SUA target levels, as recommended by the gout care guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).

Gout incidence rates from prospective cohort studies ranged from fewer than 3 new cases per 1000 person-years at < 6 mg/dl (i.e., the usual therapeutic level) to 70 new cases per 1000 person-years at SUA > 10 mg/dl. Gout recurrence risk from prospective studies ranged from about 10% at SUA < 6 mg/dl to about 50% with SUA between 6 mg/dl and 9 mg/dl; this risk was as high as 60% to 90% among those with SUA > 9 mg/dl over the study period[22,23]. Findings from

Table 3. The proportion of patients with recurrent gout, increased risk of flares, and flares per gout flare patient, according to SUA level.

Study	Period of Flare Measure, Yrs	SUA Level Category, mg/dl	Patients with Flares %	Patients with Flares Ratio of %	Flares per Gout Flare Patient, Mean (SD)
Estimates from clinically confirmed gout studies					
Perez-Ruiz, *et al*[22]	4.6 (mean)	≥ 6.0 to < 7.0	3.7	Referent	—
		≥ 7.0 to < 8.2	21.3	5.8	—
		≥ 8.3 to < 9.3	50.8	13.7	—
		≥ 9.3	61.3	16.6	—
Shoji, *et al*[23]	> 1	< 6.0	12.0	Referent	—
		≥ 6.0 to < 9.0	47.7	4.0	—
		≥ 9.0	89.5	7.5	—
Estimates from retrospective database studies					
Halpern, *et al*[34]	2	< 6.0	46.4	Referent	1.3 (0.6)
		≥ 6.0 to < 9.0	61.2	1.3	1.5 (0.8)
		≥ 9.0	63.8	1.4	1.7 (1.0)
Sarawate, *et al*[35]	5	< 6.0	23.0	Referent	—
		≥ 6.0 to < 8.0	33.0	1.4	—
		≥ 8.0	45.0	2.0	—
Wu, *et al*[36]	1	< 6.0	26.9	Referent	1.5 (0.8)
		≥ 6.0 to < 9.0	43.4	1.6	1.6 (0.9)
		≥ 9.0	54.5	2.0	1.7 (1.2)

SUA: serum uric acid.

retrospective studies showed a consistent trend regarding the graded relationship, but estimates tended to be of lower magnitude. Nonetheless, data from both retrospective and prospective studies strongly corroborate efforts to lower SUA to prevent both incident and recurrent gout, and to treat to a target of < 6 mg/dl[43]. These findings were supported by a large chart review from the United States published after completion of our current review that highlighted the inadequacy of gout management in real-world settings and the negative clinical implications of high SUA[44].

We found that relatively few prospective studies examined the relationship between SUA, incident gout, or recurrent gout flares. This paucity of relevant data may reflect the lack of research interest in the rheumatology field, given the well-established pathophysiology of gout and routine anecdotal observations in experienced rheumatology care. Regardless, our findings appear to call for further studies on the topic, to achieve a sufficient level of corresponding evidence. To that effect, because of the lack of high-quality clinical research evidence that tight control of SUA levels improves clinical outcomes in patients with gout, rheumatology guidelines have not resonated well in the gout care guidelines for primary care providers and consequently in their actual practices.

One weakness of the retrospective studies assessing gout incidence identified in our review was the incomplete ascertainment of SUA levels in a large proportion of otherwise eligible patients. Because measuring SUA is not a routine component of general clinical practice[45], it is likely that individuals without gout who had SUA measures available (even if SUA was < 6 mg/dl) would have some clinical reason for the suspicion of gout, and would therefore not be entirely representative of the unaffected (i.e., gout-free) general population. Thus, estimating outcomes based on such a non-representative, non-gout sample could bias the results. For example, Trifirò, *et al* had SUA measurements for only about 40% of the sample under study, and a rationale for why some individuals would have these measures (particularly those without gout) was not available[7]. The incidence of gout among those with SUA < 6 mg/dl observed by Trifirò, *et al* was considerably higher than estimates from other studies included in our review[16,28,29,30].

Moreover, although we identified more studies using administrative data to assess the risk of gout flares, the accuracy of their findings may be lower because clinical ascertainment of gout cases and validation of gout flares are challenging[26,34,35,36]. Most of these studies used a common approach to identify flares that involved a physician- or hospital-based claim for joint pain or gout followed by another gout-related investigation, prescription, or procedure within 7 days; however, no validation component was reported among the identified studies. This is important because estimates of the proportion of patients experiencing flares in the lowest SUA category were higher from retrospective studies compared with prospective clinical studies, although estimates of patients experiencing flares at higher SUA levels were similar between these 2 study types. This discrepancy suggests that the approach used in the retrospective studies may be overestimating the true risk of flares, particularly among those with lower SUA levels. Consequently, the incremental risk of flares at higher SUA levels from retrospective studies would be underestimated

because the risk of their baseline reference group is artificially high. These differences between prospective and retrospective studies further highlight the importance of prospective studies with an appropriate case validation component.

Strengths of our systematic review include a comprehensive approach to evidence synthesis, namely through the systematic searching of multiple biomedical databases as well as the inclusion of articles from different geographic areas, study designs, and choice of measures for SUA and definitions of gout and its flares. However, because of these broad inclusion criteria, several notable differences exist among included studies. First, SUA measures differed between studies, and some studies presented mean SUA rather than estimates according to SUA category. Even within studies that presented estimates according to SUA categories, the classifications themselves varied. Further, studies used thresholds of < 8 mg/dl or < 9 mg/dl to define an intermediate risk category, which meant that the definition for the highest SUA category would also differ between studies. Second, the timing of the SUA measure varied considerably across studies, and SUA measures occurred both prior to and following the assessment of gout incidence or recurrence. Third, because some studies did not present the number of patients for SUA subgroups and/or patients with flares, it was challenging to calculate estimates of association measures (for example, RR or IRR). Importantly, future investigations for the study question ought to involve full sets of effect estimates (both relative and absolute) according to SUA categories of narrow widths to present flexible data with which to understand and compare gout incidence and recurrence estimates. Fourth, in some studies, sample sizes within an individual SUA category were small, which would affect the precision of associated estimates of the risk of incident or recurrent gout. Finally, results from retrospective database studies included for recurrent gout may have been affected by lack of relevant information, such as increased gout flares following the initiation of ULT, the timing of SUA measurements in relation to acute attacks, and the potential influence of risk factors other than hyperuricemia. This could have contributed to the generally lower magnitude of association as compared with prospective clinical studies.

Our systematic review synthesized findings from published articles on the risk of incident and recurrent gout, and found that existing data are consistently pointing to a graded relationship in which higher SUA levels are associated with an increased risk of incident gout and recurrent flares. However, the study design, SUA categorization, and timing of the outcome measures varied substantially among included studies, calling for further evidence from prospective studies specifically designed to comprehensively evaluate these variables. Nevertheless, these findings together with the totality of the existing pathophysiologic evidence underscore the critical need to treat to SUA target levels, as recommended by the gout care guidelines from the ACR and EULAR[14,43,46].

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Perez-Ruiz F. Treating to target: a strategy to cure gout. Rheumatology 2009;48 Suppl 2:ii9-ii14.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136-41.
3. Smith EU, Díaz-Torné C, Perez-Ruiz F, March LM. Epidemiology of gout: an update. Best Pract Res Clin Rheumatol 2010;24:811-27.
4. Rho YH, Lu N, Peloquin CE, Man A, Zhu Y, Zhang Y, et al. Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study. Ann Rheum Dis 2016;75:91-5.
5. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894-900.
6. Rees F, Doherty M. Patients with gout can be cured in primary care. Practitioner 2014;258:15-9, 2.
7. Trifirò G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: a nationwide population-based study. Ann Rheum Dis 2013;72:694-700.
8. Eggebeen AT. Gout: an update. Am Fam Physician 2007;76:801-8.
9. Hosomi A, Nakanishi T, Fujita T, Tamai I. Extra-renal elimination of uric acid via intestinal efflux transporter BCRP/ABCG2. PLoS One 2012;7:e30456.
10. Luk AJ, Simkin PA. Epidemiology of hyperuricemia and gout. Am J Manag Care 2005;11 Suppl:S435-42.
11. Terkeltaub RA. Clinical practice. Gout. N Engl J Med 2003;349:1647-55.
12. Ricciuti JS, Ballinger RM, Chalkley WE. In the pipeline: FDA Advisory Committee Reviews–June 2004. [Internet. Accessed December 8, 2016.] Available from: www.medscape.com/viewarticle/482422
13. Wortmann RL. Recent advances in the management of gout and hyperuricemia. Curr Opin Rheumatol 2005;17:319-24.
14. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312-24.
15. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, García-Erauskin G, Ruiz-Lucea E. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. Ann Rheum Dis 1998;57:545-9.
16. Bhole V, De Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: fifty-two-year followup of a prospective cohort. Arthritis Rheum 2010;62:1069-76.
17. Pittman JR, Bross MH. Diagnosis and management of gout. Am Fam Physician 1999;59:1799-806, 1810.
18. STROBE. STROBE statement-checklist of items that should be included in reports of observational studies. [Internet. Accessed November 29, 2016.] Available from: www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf
19. Dalbeth N, House ME, Horne A, Petrie KJ, McQueen FM, Taylor WJ. Prescription and dosing of urate-lowering therapy, rather than

patient behaviours, are the key modifiable factors associated with targeting serum urate in gout. BMC Musculoskelet Disord 2012;13:174.
20. Khanna PP, Perez-Ruiz F, Maranian P, Khanna D. Long-term therapy for chronic gout results in clinically important improvements in the health-related quality of life: Short Form-36 is responsive to change in chronic gout. Rheumatology 2011;50:740-5.
21. Li-Yu J, Clayburne G, Sieck M, Beutler A, Rull M, Eisner E, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001;28:577-80.
22. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. Arthritis Rheum 2011;63:4002-6.
23. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321-5.
24. Strand V, Khanna D, Singh JA, Forsythe A, Edwards NL. Improved health-related quality of life and physical function in patients with refractory chronic gout following treatment with pegloticase: evidence from phase III randomized controlled trials. J Rheumatol 2012;39:1450-7.
25. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011; 306:711-20.
26. Mercieca C, Cortis P, Coleiro B, Borg AA. Concordance of gout management with European League Against Rheumatism recommendations in hospital practice. Malta Med J 2010;22:6-11.
27. Singh JA, Sarkin A, Shieh M, Khanna D, Terkeltaub R, Lee SJ, et al. Health care utilization in patients with gout. Semin Arthritis Rheum 2011;40:501-11.
28. Brauer GW, Prior IA. A prospective study of gout in New Zealand Maoris. Ann Rheum Dis 1978;37:466-72.
29. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.
30. Chen JH, Yeh WT, Chuang SY, Wu YY, Pan WH. Gender-specific risk factors for incident gout: a prospective cohort study. Clin Rheumatol 2012;31:239-45.
31. Chen JH, Pan WH, Hsu CC, Yeh WT, Chuang SY, Chen PY. Impact of obesity and hypertriglyceridemia on gout development with or without hyperuricemia: a prospective study. Arthritis Rheum Res 2013;65:133-40.
32. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol 2000;27:1501-5.
33. Maynard JW, McAdams DeMarco MA, Baer AN, Köttgen A, Folsom AR, Coresh J, et al. Incident gout in women and association with obesity in the Atherosclerosis Risk in Communities (ARIC) study. Am J Med 2012;125:717.e9-717.e17.
34. Halpern R, Fuldeore MJ, Mody RR, Patel PA, Mikuls TR. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. J Clin Rheumatol 2009;15:3-7.
35. Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol 2006;12:61-5.
36. Wu EQ, Patel PA, Mody RR, Yu AP, Cahill KE, Tang J, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? J Rheumatol 2009;36:1032-40.
37. Chan E, House ME, Petrie KJ, Horne A, Taylor WJ, Dalbeth N. Complementary and alternative medicine use in patients with gout: a longitudinal observational study. J Clin Rheumatol 2014;20:16-20.
38. Dalbeth N, House ME, Horne A, Te Karu L, Petrie KJ, McQueen FM, et al. The experience and impact of gout in Māori and Pacific people: a prospective observational study. Clin Rheumatol 2013;32:247-51.
39. Khanna D, Sarkin AJ, Khanna PP, Shieh MM, Kavanaugh AF, Terkeltaub RA, et al. Minimally important differences of the gout impact scale in a randomized controlled trial. Rheumatology 2011;50:1331-6.
40. Perez-Ruiz F, Martínez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis 2014;73:177-82.
41. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis 2013;72:826-30.
42. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661-7.
43. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al; American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.
44. Khanna P, Khanna D, Storgard C, Baumgartner S, Morlock R. A world of hurt: failure to achieve treatment goals in patients with gout requires a paradigm shift. Postgrad Med 2016;128:34-40.
45. Terkeltaub R. Update on gout: new therapeutic strategies and options. Nat Rev Rheumatol 2010;6:30-8.
46. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al; British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology 2007;46:1372-4.