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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

ABSTRACT

Introduction Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

Methods The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

Results A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2 = 99.7%$). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2=86.3%$) for self-report and 63% (95% CI, 42%-83%, $I^2 = 82.9%$) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

Conclusions Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that rheumatologists should

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7 pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among
8 adult gout patients.
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11 **KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis
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13 14 **ARTICLE SUMMARY**

15 16 **Strengths and limitations of this study**

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20 ➤ To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
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22 ➤ This systematic review was composed of 22 studies, with 137699 gout patients.
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25 ➤ Some limitations should be considered: a substantial amount of the heterogeneity among the studies remained unexplained by the variables
26 examined; our search did not include the EMBASE database and Cochrane database library. Moreover, several studies that referred to
27 medications unspecified ULT were excluded, which could bias the findings.
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INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate MSU in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide¹. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes². It has been widely certified that treatment with ULT is key to successful long-term management of gout³. Therefore, lifelong ULT prescription is usually advised, but the prospect of lifelong therapy may contribute to very low adherence rate⁴. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment⁵. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies⁶. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.

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METHODS

The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as closely as possible^{7, 8}.

Search strategy

The systematic review examined the English-language databases of PubMed and Web of Science, and Chinese databases of the CNKI Scholar and WanFang databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy.

Different search strategies were combined, as follows. For the English-language databases, search details were (adherence [All Fields] OR (“patient compliance” [MeSH Terms] OR (“patient” [All Fields] AND “compliance” [All Fields]) OR “patient compliance” [All Fields] OR “compliance” [All Fields] OR “compliance” [MeSH Terms])) AND (urate-lowering [All Fields] AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“gout” [MeSH Terms] OR “gout” [All Fields])). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of

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7 selected articles were also searched to identify additional reports.
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9 **Inclusion and exclusion criteria**

10 Inclusion criteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the
11 articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.
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15 Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to
16 search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints, or
17 non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used the term
18 “adherence,” but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout could not
19 be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication); (7) papers from
20 which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of compliance was
21 determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).
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35 **Data extraction and quality assessment**

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37 Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not met the inclusion
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8 criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final
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10 studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following
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12 information was independently extracted from each article by other two trained investigators using a standardized form: year, sample size,
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14 population, country, average age of participants, percentage of male participants, mean disease duration, type of medication, outcome, criteria for
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16 detection of adherence/compliance, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered
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18 multiple measurements from the same study, the most commonly evaluation method was used to carry out analysis. All the methods were used
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20 for subgroup analysis if not in the same subgroup. The methodological quality of each study included in the present meta-analysis was assessed
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22 using a modified version of the Newcastle-Ottawa Scale⁹. Studies were judged to be at low risk of bias (≥ 3 points) or high risk of bias (< 3 points).
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27 Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a
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30 third reviewer.

31 32 **Outcome measures**

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35 The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days
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37 covered (PDC)], pill count, self-report or interview.
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Statistical analysis

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients¹⁰. Between-study heterogeneity was assessed by the I^2 with thresholds of $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$ indicating low, moderate and high heterogeneity, respectively¹¹. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis^{12, 13}. Statistical analyses were performed with STATA version 12.0. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

RESULTS

Study selection

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

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Study characteristics

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims¹⁴⁻²⁸, with the cutpoint of $\geq 80\%$. One used prescription claim and self report²⁹, one article used pill count³⁰; two used self-report^{31, 32} and three articles assessed by interview³³⁻³⁵. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points³¹, 13 received 4 points^{14-18, 21-28}, 1 received 3 points¹⁹, 5 received 2 points^{20, 29, 30, 33, 34}, and 2 received 1 point^{32, 35}.

Table 1A. Baseline characteristics.

Studies	N (total)	N (ULT)	Population, Country	Disease			Medications	Quality
				Age, Yrs, Mean (SD)	Male,(%)	Duration,Yrs, Mean (SD)		
Prescription claims								
Sarawate et al, 2006	5942	2405	Managed care database, USA	57.4(14.1)*	76.4*	NS	allopurinol	4

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7	Briesacher et al, 2008	9715	MEDSTAT database, USA	58.7(0.14)	77.5	NS	allopurinol, uricosurics	4	
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10									
11	Harrold et al, 2009	4166	Integrated delivery Systems, USA	62 (14)	75	NS	allopurinol, probenecid,	4	
12							sulfinpyrazone		
13									
14									
15	Halpern et al, 2009	18243	10070	Claims database, USA	Mean 53.9	84.2	NS	allopurinol	4
16									
17	Rashid et al, 2012		9288	KPSC health care, USA	Mean 60	78	NS	allopurinol	4
18									
19									
20									
21	Horsburgh et al, 2014	27,243	732	Community pharmacy dispensing	NA	39.5 †	NS	allopurinol	4
22									
23									
24									
25	Singh, 2014		43	Outpatient clinic, USA	63.9 (9.9)	67	NS	allopurinol, febuxostat	2
26									
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30	McGowan et al, 2016	34634	15908	HSE-PCRS scheme database, Ireland	Mean 65.2*	73*	NS	probenecid,	3
31									
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35	Tan et al, 2016		91	Hospital clinics, Singapore	53.5(16.9)	92.3	NS	allopurinol, probenecid	2
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38	Solomon et al, 2008		9823	Medicare and PACE enrollees, USA	Mean 79	28 †	NS	allopurinol	4
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8							allopurinol, febuxostat,	
9	Park et al, 2012	352	242	Scott & White Health Plan, USA	61.02(15.33)*	72.4* †	NS	4
10							probenecid	
11								
12	Zandman-Goddard et al, 2013		7644	MHS database, Israel	NA	72	NS	4
13							allopurinol	
14								
15	Mantarro et al, 2015		3727	HSD database, Italy	Mean 65	80	NS	4
16								
17				Clinical and administrative				
18	Rashid et al, 2015		8288	databases, USA	NA	79.80	NS	4
19							allopurinol, febuxostat,	
20							probenecid	
21								
22	Kuo et al, 2015		49395	GPRD database, UK	NA	NA	NS	4
23							ULT	
24								
25	Riedel et al, 2004	9482	5597	IPA plans, USA	51(11)*	82.1*	NS	4
26							allopurinol	
27	Pill counts							
28								
29								
30	Lee et al, 2016		132	Outpatient clinic, Korea	51.9 (10.4)	100	100.0(89.1) [§]	2
31							allopurinol, febuxostat	
32	Self-report							
33								
34								
35							allopurinol,	
36	Silva et al, 2010		34	Outpatient, Spain	57.1(11.8)	94.1 †	NS	1
37							benzbromarone	
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People visiting the Gout and Uric								
Singh et al, 2016	499	251	Acid Education Society's website, USA	56.3(12.6)*	73.7*	NS	allopurinol, febuxostat	5
Interview								
Martini et al, 2012	60	56	Community pharmacies, New Zealand	Mean 61*	90*	NS	allopurinol	2
Sheng et al, 2014	161	80 †	Gout Clinic, China	NA	NA	NS	ULD	1
van Onna et al, 2015	15	12	Outpatient clinic and primary care practices, The Netherlands	63(12)*	93.3* †	11(7)*	ULT	2

*data for total population; †Calculated based on data provided in the article. §disease duration(months)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

Table 1B. Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

Studies	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence %
Prescription claims				
Sarawate et al, 2006	compliance	MPR was calculated as medication supply actually received divided by medication supply that could have been received.	MPR \geq 80 %	28
Briesacher et al, 2008	adherence	MPR defined as the days' supply of the drug dispensed during the follow-up year divided by the number of days in the year.	MPR \geq 80 %	36.8
Harrold et al, 2009	adherence	MPR defined as the days supply of medication dispensed during the follow-up year divided by the number of days in the year and is a reliable measure of adherence.	MPR \geq 80 %	44
Halpern et al, 2009	compliance	MPR: sum of days supply from first observed allopurinol fill during the 2-year observation period]/[number of days between the first observed fill and the end of the post-index period.	MPR \geq 80 %	44
Rashid et al, 2012	adherence	Adherence was measured using the MPR over the follow up time period.	MPR $>$ 80 %	47.5 [†]

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7		MPR defined as the ratio of days supplied from initial dispensing to the number of		
8	Horsburgh et al, 2014	adherence	MPR $\geq 80\%$	78†
9		days to the end of the study period or the patient's date of death.		
10				
11				
12	Singh, 2014	adherence	MPR ≥ 0.80	32.6†
13		Self-report adherence to ULT.		
14				
15		MPR defined as the number of doses filled by the pharmacist divided by the		
16	McGowan et al, 2016	adherence	MPR $\geq 80\%$	45.5
17		number of days in the defined period (6 or 12 months).		
18				
19				
20	Tan et al, 2016	adherence	MPR $\geq 80\%$	83.5
21		MPR summarized the proportion of days a patient has a supply of medications for.		
22				
23		PDC was calculated as the days with available UALT divided by the total number		
24	Solomon et al, 2008	adherence	PDC $\geq 80\%$	36†
25		of days of follow-up.		
26				
27		PDC defined as the number of days during the study period (365 days) that the		
28	Park et al. 2012	adherence	PDC $\geq 80\%$	26.9†
29		patient had at least 1 gout-specific medication on hand.		
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32		Mean PDC calculated by dividing the quantity of allopurinol dispensed by the total		
33	Zandman-Goddard et al,			
34		adherence	PDC $\geq 80\%$	17
35		time interval from index date to drug cessation, death, leaving MHS or 31		
36	2013	December 2009, whichever occurred first.		
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7		PDC defined as dividing the cumulative days of medication use by the length of		
8	Mantarro et al, 2015	adherence	PDC \geq 80%	45.9
9		follow up.		
10				
11		PDC was defined as the number of days with ULT drug dispensed divided by the		
12	Rashid et al, 2015	adherence	PDC \geq 80%	48.2†
13		number of days in the specified time interval (365 days).		
14				
15		PDC defined as the period from the latest of registration date or 1 January to the		
16	Kuo et al, 2015	adherence	PDC \geq 80%	39.66
17		earliest of transfer-out, death date or 31 December of the calendar year specified.		
18				
19		Compliance was defined for each prescription period as the presumed use of		
20	Riedel et al, 2004	compliance	Compliance rate \geq 80%	18
21		allopurinol on at least 80% of the days of that period.cc		
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30	Lee et al, 2016	compliance	Pill count \geq 80%	71.2
31		Pill counts: noncompliance was defined as <80% of the prescribed dose taken.		
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35	Silva et al, 2010	compliance	NS	53†
36		Compliance defined as taking medication regularly, as prescribed.		
37				
38	Singh et al, 2016	adherence	Adherence >0.80	78.5
39		Number of days the patient forgot to take ULT in the last month.		
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			MMAS-8 score \geq 6	
Tan et al, 2016	adherence	MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8)	(75%)	61.9
Interview				
Martini et al, 2012	compliance	Participants admitted to not taking ULTs as prescribed.	NS	79
Sheng et al, 2014	adherence	Adherence was defined as sustained use of ULD in the prior 12 months, otherwise non-adherence.	NS	53.8 [†]
van Onna et al, 2015	adherence	Non-adherence at some point in time was defined as admission in the interview.	NS	50.0 [†]

[†]Calculated based on data provided in the article.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky Medication Adherence Scale; NS: not stated

The rate of adherence to ULT among gout patients.

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2 = 99.7\%$) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8\%$) according to

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7 prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2 = 86.3\%$) for self-report and 63%
8 (95% CI, 42%-83%, $I^2 = 82.9\%$) for interview, respectively (Figure 2).
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10 11 **Sensitivity and subgroup analyses**

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14 Sensitivity analysis indicated that all of the estimated values were in regions of the lower CI limit and upper CI limit, showed that our results
15 were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2.
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19 The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of
20 origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality. The results of the meta-analysis affected by the
21 country of origin in those included studies, showed that studies from the Oceania had higher adherence estimates [78% (95% CI, 75%–81%) vs
22 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The
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30 subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall
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34 quality showed no clear patterns.

35 **Table 2.** Summary of adherence rate and heterogeneity findings.
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Outcomes	No. of studies	No. of participants	Adherence, % (95%	Heterogeneity		Test for overall effect	
			confidence intervals)	<i>P</i> -value	<i>I</i> ² (%)	<i>Z</i>	<i>P</i> -value
Overall	22	137699	47(42, 52)	0.000	99.7	18.66	0.000
Measurement methods							
Prescription claims	16	137134	42(37, 47)	0.000	99.8	15.61	0.000
Pill count	1	132	71(63, 79)	-	-	18.06	0.000
Self-report	3	376	66(50, 81)	0.001	86.3	8.40	0.000
Interview	3	148	63(42,83)	0.003	82.9	6.09	0.000
Publication Year							
2010s	6	41766	34(26, 43)	0.000	99.7	8.22	0.000
2010-	16	95923	53(47, 60)	0.000	99.7	15.95	0.000
Country of origin							
America	11	59888	40(33, 47)	0.000	99.6	11.82	0.000

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Oceania	2	788	78(75, 81)	0.860	0	52.97	0.000
Europe	5	69076	44(40, 49)	0.000	98.0	19.62	0.000
Asia	4	7947	56(17, 96)	0.000	99.4	2.81	0.000
Data sources							
Database	14	13700	40(34, 45)	0.000	99.8	13.48	0.000
Non-database	8	699	65(54, 75)	0.000	89.2	11.81	0.000
Representativeness							
Multiple sites	17	137319	44(39, 50)	0.000	99.8	15.79	0.000
A single site	5	380	60(43, 76)	0.000	92.1	7.04	0.000
Sample size							
≥ 200	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
< 200	7	448	62(48, 75)	0.000	89.3	9.12	0.000
Cutpoint							

≥80%	18	137517	45(40, 51)	0.000	99.7	16.70	0.000
≥75%	1	19	62(52, 72)	0.004	77.8	7.54	0.000
NS	4	182	60(45, 76)	-	-	12.16	0.000
Quality							
≥3 points	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
<3points	7	448	62(48, 75)	0.000	89.3	9.12	0.000

Publication bias

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), $P = 0.356$; Egger: bias = 4.32 (95% CI: -16.55, 25.18), $P = 0.664$; Egger: bias = -4.92 (95% CI: -20.50, 10.66), $P = 0.155$; Egger: bias = -2.02 (95% CI: -70.13, 66.08), $P = 0.770$, respectively] (Figure not shown).

DISCUSSION

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7 This systematic review and meta-analysis of 22 studies involving 137699 adult gout patients demonstrated that overall, 47% of adult gout
8 patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were presented in 42% among gout patients.
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10 The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview, respectively. Additionally, our analysis found no
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12 statistical differences among the different methods. To our knowledge, the meta-analysis is the first to quantify adherence and to seek a
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14 relationship between adherence and the method used to measure it.
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20 A previous systematic review included 16 studies⁶. We identified an additional studies. Importantly, the previous review did not quantify
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22 adherence. In our meta-analysis, most studies used a cutpoint of $\geq 80\%$ to define adherent patients. Data on persistence, discontinuation,
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24 switching, treatment gap or retention rate, and adherence to nonmedical therapy were excluded.
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28 The results demonstrated an overall adherence rate to ULT in adult gout patients of 47%. However, heterogeneity was large. By subgroup
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30 analysis for measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and
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32 overall quality in those included studies, country of origin was found to contributed to the heterogeneity between studies, with heterogeneity of
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34 0% among studies from Oceania, 99.6% from America, 98.0% from Europe, and 99.4% from Asia. Although studies varied widely in terms of
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36 quality, our sensitivity analyses suggested that adherence rate estimates were reasonably stable.
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7 There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed.
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9 First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as
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11 gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, our search did not
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13 include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified ULT were excluded,
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15 which could bias the findings.
16

17 18 **CONCLUSION**

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20 The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that rheumatologists should pay
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22 more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult
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24 gout patients.
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27 28 **Acknowledgments**

29
30 We would like to thank Yuwei Gu and Guo Zhang for their great assistance with this study.
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32

33 34 **Competing interests**

35
36 The authors declared that they have no competing interests.
37

38 39 **Funding**

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8
9 Provincial Commission of Health and Family Planning Foundation (Grant no. H201317 and H201623); Science Foundation of Nantong City
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12
13 HS2016003).
14
15

16 17 **Authors' contributions**

18
19 RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality,
20
21 analyzed the data and wrote the draft of the paper. YC, LZ, QZ, TF, HC, LL, and ZG gave advice on meta-analysis methodology and revised the
22
23 paper. All authors contributed to reviewing or revising the paper. LL and ZG were the guarantors of this work and had full access to all the data
24
25 in the study and took responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final manuscript.
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30 **Ethics approval and consent to participate**

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32 Ethical approval and consent to participate are not required for this review.
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7 **Figure 1.** Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15
8 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were
9 excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies
10 were included in the quantitative synthesis (meta-analysis).
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15 **Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.
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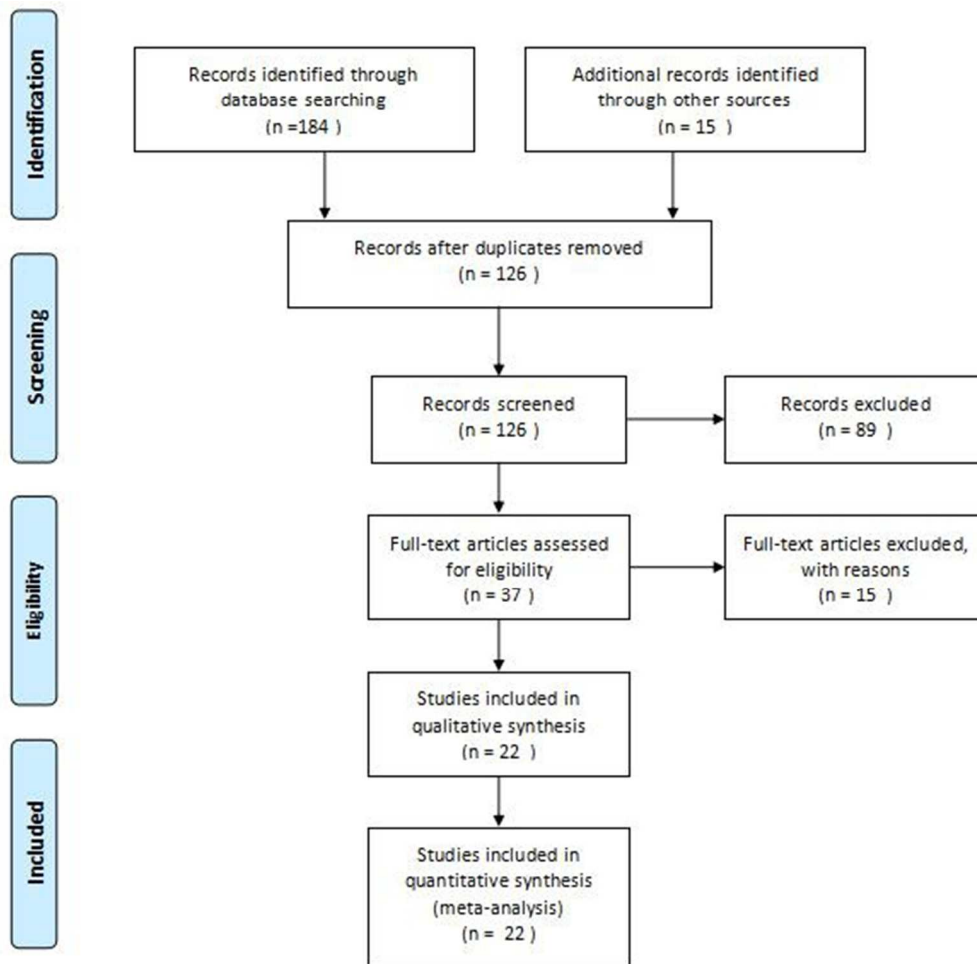


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

155x151mm (96 x 96 DPI)

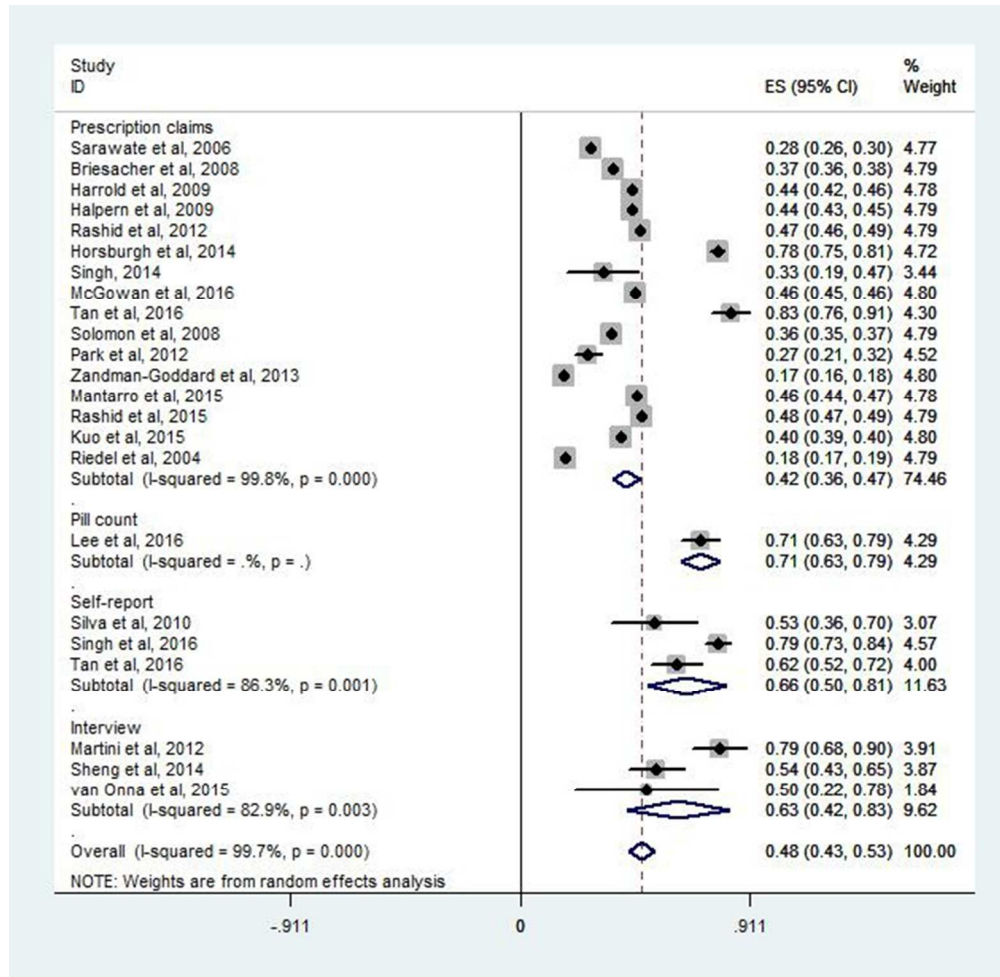


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

166x162mm (96 x 96 DPI)



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NO
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NO
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22-23
Sponsor	5b	Provide name for the review funder and/or sponsor	NO
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NO
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-6

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Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9-17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	17-20
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NO
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	adherence, urate-lowering therapy, gout, meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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Word count: 2486

The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

ABSTRACT

Introduction Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

Methods The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

Results A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2 = 99.7\%$). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8\%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2=86.3\%$) for self-report, and 63% (95% CI, 42%-83%, $I^2 = 82.9\%$) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

Conclusions Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay

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7 more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult
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9 gout patients.
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11 **Strengths and limitations**

- 14 ➤ To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
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- 16 ➤ This systematic review was composed of 22 studies, with 137699 gout patients.
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- 18 ➤ A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
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- 20 ➤ EMBASE database and Cochrane database library were not searched due to lack of access.
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- 22 ➤ Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.
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27 **KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis
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INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide¹. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes². Previous studies have reported that effective ULT to reduce SU levels sufficiently to prevent further crystal formation and to dissolve existing urate crystals, thus eliminating the causative agent, making gout the only chronic arthritis that can be “cured”³⁻⁵. Therefore, lifelong ULT prescription, the key to successful long-term management of gout⁶, is usually advised. But the prospect of lifelong therapy may contribute to very low adherence rate⁷. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment⁸. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies⁹. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

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7 To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for
8 different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.
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10 11 **METHODS**

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14 The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses
15 (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as closely as possible^{10,11}.
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18 19 **Search strategy**

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21 The systematic review examined the English-language databases of PubMed and Web of Science, and Chinese databases of the CNKI Scholar
22 and WanFang databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists
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24 were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles
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26 and to test the search strategy.
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31 Different search strategies were combined, as follows. For the English-language databases, search details were (adherence [All Fields] OR
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33 (“patient compliance” [MeSH Terms] OR (“patient” [All Fields] AND “compliance” [All Fields]) OR “patient compliance” [All Fields] OR
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35 “compliance” [All Fields] OR “compliance” [MeSH Terms])) AND (urate-lowering [All Fields] AND (“therapy” [Subheading] OR “therapy”
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7 [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“gout” [MeSH Terms] OR “gout” [All Fields])). For the
8 Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of
9 selected articles were also searched to identify additional reports.
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14 **Inclusion and exclusion criteria**

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17 Inclusion criteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the
18 articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.
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22 Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to
23 search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints,
24 diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used
25 the term “adherence,” but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout
26 could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication); (7)
27 papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of
28 compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).
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Data extraction and quality assessment

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not meet the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: year, sample size, population, country, average age of participants, percentage of male participants, mean disease duration, type of medication, outcome, criteria for detection of adherence/compliance, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly evaluation method was used to carry out analysis. All the methods were used for subgroup analysis if not in the same subgroup. The methodological quality of each study included in the present meta-analysis was assessed using a modified version of the Newcastle-Ottawa Scale¹². Studies were judged to be at low risk of bias (≥ 3 points) or high risk of bias (< 3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

Outcome measures

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7 The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days
8 covered (PDC)], pill count, self-report or interview.
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10 11 **Statistical analysis**

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14 Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study
15 heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients¹³. Between-study
16 heterogeneity was assessed by the I^2 with thresholds of $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$ indicating low, moderate and high heterogeneity, respectively¹⁴.
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20 The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses.
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23 Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources,
24 representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and
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30 Egger's test were combined to explore the potential publication bias in this meta-analysis^{15, 16}. Regression analysis was performed to test the
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36 difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The
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49 statistical significance level was 0.05, except for the test of between-study heterogeneity.

37 **RESULTS**

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Study selection

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

Study characteristics

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims¹⁷⁻³¹, with the cutpoint of ≥80%. One used prescription claim and self report³², one article used pill count³³; two used self-report^{34, 35} and three articles assessed by interview³⁶⁻³⁸. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points³⁴, 13 received 4 points^{17-21, 24-31}, 1 received 3 points²², 5 received 2 points^{23, 32, 33, 36, 37}, and 2 received 1 point^{35, 38}.

Table 1A. Baseline characteristics.

Studies	N (total)	N (ULT)	Population, Country	Age, Yrs, Mean (SD)	Male,(%)	Disease Duration,Yrs,	Medications	Quality
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							Mean (SD)		
Prescription claims									
Sarawate et al, 2006	5942	2405	Managed care database, USA	57.4(14.1)*	76.4*	NS	allopurinol	4	
Briesacher et al, 2008		9715	MEDSTAT database, USA	58.7(0.14)	77.5	NS	allopurinol, uricosurics	4	
Harrold et al, 2009		4166	Integrated delivery Systems, USA	62 (14)	75	NS	allopurinol, probenecid, sulfinpyrazone	4	
Halpern et al, 2009	18243	10070	Claims database, USA	Mean 53.9	84.2	NS	allopurinol	4	
Rashid et al, 2012		9288	KPSC health care, USA	Mean 60	78	NS	allopurinol	4	
Horsburgh et al, 2014	27,243	732	Community pharmacy dispensing databases, New Zealand	NA	39.5 †	NS	allopurinol	4	
Singh, 2014		43	Outpatient clinic, USA	63.9 (9.9)	67	NS	allopurinol, febuxostat	2	
McGowan et al, 2016	34634	15908	HSE-PCRS scheme database, Ireland	Mean 65.2*	73*	NS	allopurinol, febuxostat, probenecid,	3	

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							sulfinpyrazone	
Tan et al, 2016	91	Hospital clinics, Singapore	53.5(16.9)	92.3	NS	allopurinol, probenecid	2	
Solomon et al, 2008	9823	Medicare and PACE enrollees, USA	Mean 79	28 †	NS	allopurinol	4	
Park et al. 2012	352	242	Scott & White Health Plan, USA	61.02(15.33)*	72.4* †	NS	allopurinol, febuxostat, probenecid	4
Zandman-Goddard et al, 2013	7644	MHS database, Israel	NA	72	NS	allopurinol	4	
Mantarro et al, 2015	3727	HSD database, Italy	Mean 65	80	NS	allopurinol	4	
Rashid et al, 2015	8288	Clinical and administrative databases, USA	NA	79.80	NS	allopurinol, febuxostat, probenecid	4	
Kuo et al, 2015	49395	GPRD database, UK	NA	NA	NS	ULT	4	
Riedel et al, 2004	9482	5597	IPA plans, USA	51(11)*	82.1*	NS	allopurinol	4
Pill counts								
Lee et al, 2016	132	Outpatient clinic, Korea	51.9 (10.4)	100	100.0(89.1) [§]	allopurinol, febuxostat	2	

Self-report

Silva et al, 2010	34		Outpatient, Spain	57.1(11.8)	94.1 †	NS	allopurinol, benzbromarone	1
			People visiting the Gout and Uric Acid Education Society's website,	56.3(12.6)*	73.7*	NS	allopurinol, febuxostat	5
Singh et al, 2016	499	251	USA					

Interview

Martini et al, 2012	60	56	Community pharmacies, New Zealand	Mean 61*	90*	NS	allopurinol	2
Sheng et al, 2014	161	80 †	Gout Clinic, China	NA	NA	NS	ULD	1
van Onna et al, 2015	15	12	Outpatient clinic and primary care practices, The Netherlands	63(12)*	93.3* †	11(7)*	ULT	2

*data for total population; †Calculated based on data provided in the article. §disease duration(months)

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ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

Table 1B. Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

Studies	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence %
Prescription claims				
Sarawate et al, 2006	compliance	MPR was calculated as medication supply actually received divided by medication supply that could have been received.	MPR \geq 80 %	28
Briesacher et al, 2008	adherence	MPR defined as the days' supply of the drug dispensed during the follow-up year divided by the number of days in the year.	MPR \geq 80 %	36.8
Harrold et al, 2009	adherence	MPR defined as the days supply of medication dispensed during the follow-up year divided by the number of days in the year and is a reliable measure of adherence.	MPR \geq 80 %	44
Halpern et al, 2009	compliance	MPR: sum of days supply from first observed allopurinol fill during the 2-year	MPR \geq 80 %	44

		observation period]/[number of days between the first observed fill and the end of		
		the post-index period.		
Rashid et al, 2012	adherence	Adherence was measured using the MPR over the follow up time period.	MPR >80 %	47.5†
Horsburgh et al, 2014	adherence	MPR defined as the ratio of days supplied from initial dispensing to the number of days to the end of the study period or the patient's date of death.	MPR ≥80 %	78†
Singh, 2014	adherence	Self-report adherence to ULT.	MPR ≥0.80	32.6†
McGowan et al, 2016	adherence	MPR defined as the number of doses filled by the pharmacist divided by the number of days in the defined period (6 or 12 months).	MPR ≥80 %	45.5
Tan et al, 2016	adherence	MPR summarized the proportion of days a patient has a supply of medications for.	MPR ≥80 %	83.5
Solomon et al, 2008	adherence	PDC was calculated as the days with available UALT divided by the total number of days of follow-up.	PDC ≥ 80%	36†
Park et al. 2012	adherence	PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand.	PDC ≥ 80%	26.9†

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		Mean PDC calculated by dividing the quantity of allopurinol dispensed by the total		
Zandman-Goddard et al, 2013	adherence	time interval from index date to drug cessation, death, leaving MHS or 31 December 2009, whichever occurred first.	PDC \geq 80%	17
Mantarro et al, 2015	adherence	PDC defined as dividing the cumulative days of medication use by the length of follow up.	PDC \geq 80%	45.9
Rashid et al, 2015	adherence	PDC was defined as the number of days with ULT drug dispensed divided by the number of days in the specified time interval (365 days).	PDC \geq 80%	48.2†
Kuo et al, 2015	adherence	PDC defined as the period from the latest of registration date or 1 January to the earliest of transfer-out, death date or 31 December of the calendar year specified.	PDC \geq 80%	39.66
Riedel et al, 2004	compliance	Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc	Compliance rate \geq 80%	18
Pill count				
Lee et al, 2016	compliance	Pill counts: noncompliance was defined as <80% of the prescribed dose taken.	Pill count \geq 80%	71.2

Self-report

10	Silva et al, 2010	compliance	Compliance defined as taking medication regularly, as prescribed.	NS	53 [†]
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12	Singh et al, 2016	adherence	Number of days the patient forgot to take ULT in the last month.	Adherence >0.80	78.5
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14				MMAS-8 score ≥ 6	
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16	Tan et al, 2016	adherence	MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8)		61.9
17				(75%)	
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23	Martini et al, 2012	compliance	Participants admitted to not taking ULTs as prescribed.	NS	79
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25					
26	Sheng et al, 2014	adherence	Adherence was defined as sustained use of ULD in the prior 12 months, otherwise	NS	53.8 [†]
27			non-adherence.		
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30	van Onna et al, 2015	adherence	Non-adherence at some point in time was defined as admission in the interview.	NS	50.0 [†]

[†]Calculated based on data provided in the article.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky

Medication Adherence Scale; NS: not stated

The rate of adherence to ULT among gout patients.

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2 = 99.7%$) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2 = 86.3%$) for self-report and 63% (95% CI, 42%-83%, $I^2 = 82.9%$) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P = 0.535$).

Sensitivity and subgroup analyses

Sensitivity analysis indicated that all of the estimated values were in regions of the lower CI limit and upper CI limit, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality. The results of the meta-analysis affected by the country of origin in those included studies, showed that studies from the Oceania had higher adherence estimates [78% (95% CI, 75%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

Table 2. Summary of adherence rate and heterogeneity findings.

Outcomes	No. of studies	No. of participants	Adherence, % (95%	Heterogeneity		Test for overall effect	
			confidence intervals)	<i>P</i> -value	<i>I</i> ² (%)	<i>Z</i>	<i>P</i> -value
Overall	22	137699	47(42, 52)	0.000	99.7	18.66	0.000
Measurement methods							
Prescription claims	16	137134	42(37, 47)	0.000	99.8	15.61	0.000
Pill count	1	132	71(63, 79)	-	-	18.06	0.000
Self-report	3	376	66(50, 81)	0.001	86.3	8.40	0.000
Interview	3	148	63(42,83)	0.003	82.9	6.09	0.000
Publication Year							
2010s	6	41766	34(26, 43)	0.000	99.7	8.22	0.000

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2010-	16	95923	53(47, 60)	0.000	99.7	15.95	0.000
Country of origin							
America	11	59888	40(33, 47)	0.000	99.6	11.82	0.000
Oceania	2	788	78(75, 81)	0.860	0	52.97	0.000
Europe	5	69076	44(40, 49)	0.000	98.0	19.62	0.000
Asia	4	7947	56(17, 96)	0.000	99.4	2.81	0.000
Data sources							
Database	14	13700	40(34, 45)	0.000	99.8	13.48	0.000
Non-database	8	699	65(54, 75)	0.000	89.2	11.81	0.000
Representativeness							
Multiple sites	17	137319	44(39, 50)	0.000	99.8	15.79	0.000
A single site	5	380	60(43, 76)	0.000	92.1	7.04	0.000
Sample size							

≥ 200	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
< 200	7	448	62(48, 75)	0.000	89.3	9.12	0.000
Cutpoint							
≥80%	18	137517	45(40, 51)	0.000	99.7	16.70	0.000
≥75%	1	19	62(52, 72)	0.004	77.8	7.54	0.000
NS	4	182	60(45, 76)	-	-	12.16	0.000
Quality							
≥3 points	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
<3points	7	448	62(48, 75)	0.000	89.3	9.12	0.000

Publication bias

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), $P = 0.356$; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

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7 $P = 0.664$; Egger: bias = -4.92 (95% CI: $-20.50, 10.66$), $P = 0.155$; Egger: bias = -2.02 (95% CI: $-70.13, 66.08$), $P = 0.770$, respectively] (Figure
8 not shown).
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10 11 **DISCUSSION**

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14 To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence
15 and to seek a relationship between adherence and the method used to measure it.
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19 Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were
20 presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview,
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22 respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, self-report, interview,
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24 and prescription claims. Although no statistical differences were found among the different methods, suboptimal medication adherence was clear
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26 across the included studies. It is particularly shocking that the adherence rate of 42% based on prescription claims and the overall adherence rate
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28 of 47% are below the well-quoted WHO estimate that 50% of adults adhere to long-term therapies.
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35 A previous systematic review included 16 studies⁹. We identified an additional studies. Importantly, the previous review did not quantify
36 adherence. In our meta-analysis, most studies used a cutpoint of $\geq 80\%$ to define adherent patients. Data on persistence, discontinuation,
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7 switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.
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10 The results demonstrated an overall adherence rate to ULT in adult gout patients of 47%. However, heterogeneity was large. By subgroup
11 analysis for measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and
12 overall quality in those included studies, country of origin was found to contributed to the heterogeneity between studies, with heterogeneity of
13 0% among studies from Oceania, 99.6% from America, 98.0% from Europe, and 99.4% from Asia. Although studies varied widely in terms of
14 quality, our sensitivity analyses suggested that adherence rate estimates were reasonably stable.
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22 This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from UK. The
23 reasons for this could be that interview studies or postal surveys are prompting patients to self-report higher adherence. Additionally, adherence
24 also depends on the healthcare system in which the study is done - private (with billing for drugs used) vs. government funded; primary care vs.
25 secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the
26 findings.
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35 Because of the low adherence with ULT, it is particularly important to carry out potential interventions to achieve improved gout-related
36 outcomes. These interventions include initiation of prophylactic anti-inflammatory medication when starting ULT, frequent follow-ups, regular
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7 serum urate monitoring and improved patient education, which can be achieved through pharmacist- or nurse-assisted programs³⁹. Abhishek
8 Abhishek et al⁴⁰ and Rees et al⁴¹ have confirmed that there are excellent adherence rates after nurse led treatment of gout, which means that
9 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.
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15 There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed.
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17 First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as
18 gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access,
19 our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified
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ULT were excluded, which could bias the findings.

CONCLUSION

The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

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9 **Competing interests**

10 The authors declared that they have no competing interests.
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23 HS2016003).
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27 **Authors' contributions**

28
29 RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality,
30
31 analyzed the data and wrote the draft of the paper. GZ, YC, LZ, QZ, TF, HC, LL, and ZG gave advice on meta-analysis methodology and revised
32
33 the paper. All authors contributed to reviewing or revising the paper. LL and ZG were the guarantors of this work and had full access to all the
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35 data in the study and took responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final
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10 **Ethics approval and consent to participate**

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12 Ethical approval and consent to participate are not required for this review.

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For peer review only

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7 **Figure 1.** Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15
8 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were
9 excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies
10 were included in the quantitative synthesis (meta-analysis).
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15 **Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.
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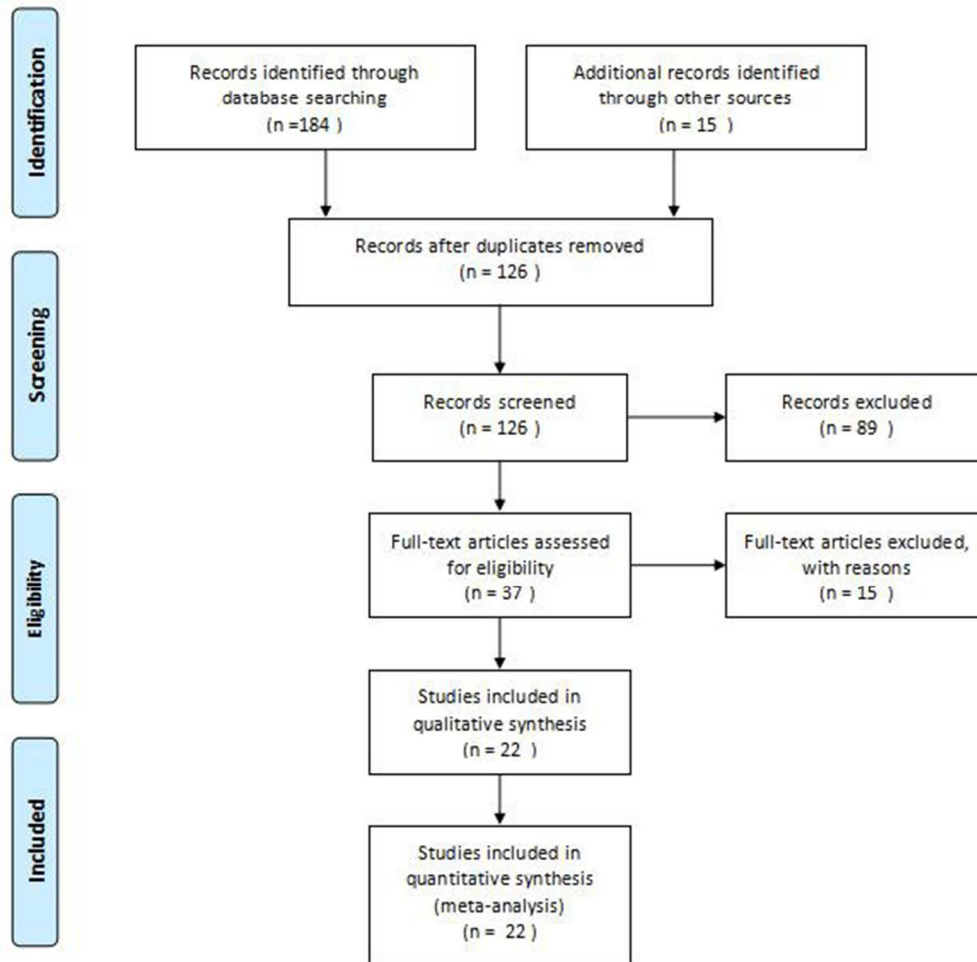


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

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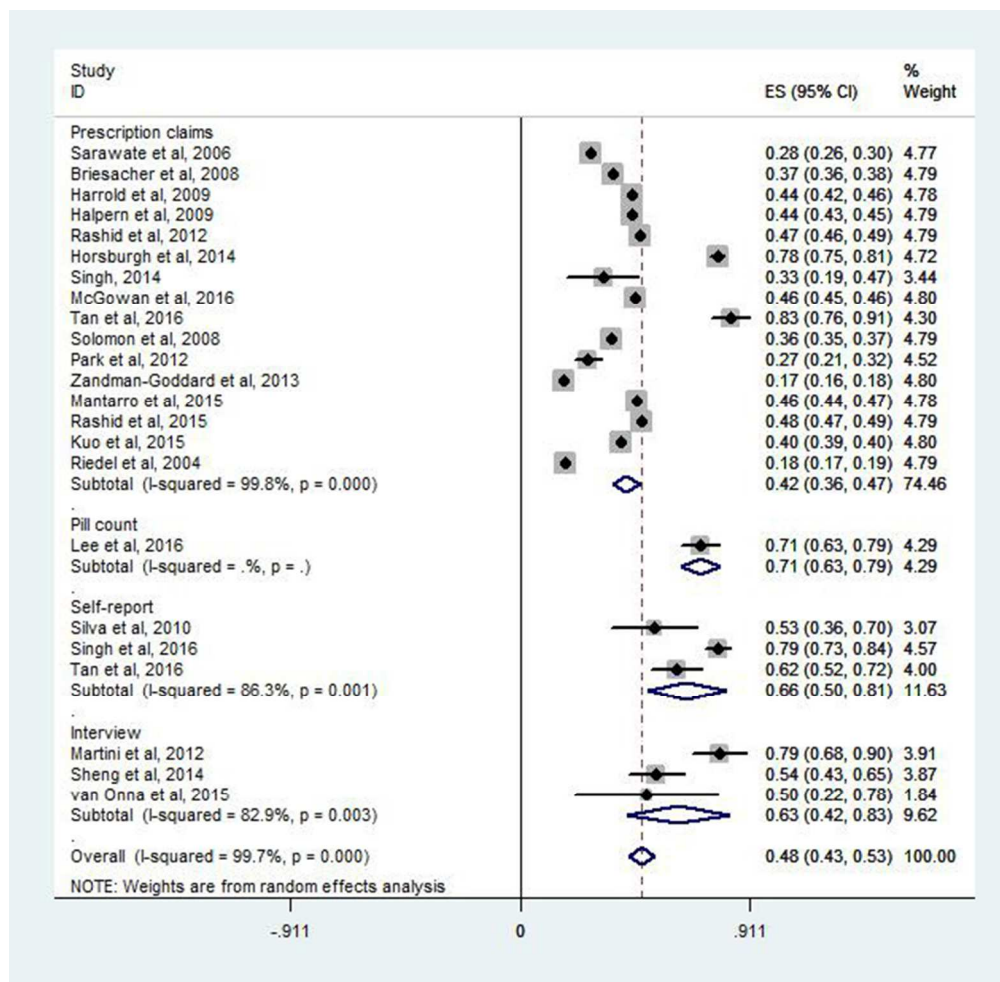


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

53x52mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NO
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NO
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NO
Support:			
Sources	5a	Indicate sources of financial or other support for the review	24
Sponsor	5b	Provide name for the review funder and/or sponsor	NO
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NO
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9-17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	17-20
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NO
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20-21
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

ABSTRACT

Introduction Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

Methods The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

Results A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2 = 99.7\%$). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8\%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2=86.3\%$) for self-report, and 63% (95% CI, 42%-83%, $I^2 = 82.9\%$) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

Conclusions Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay

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7 more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult
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9 gout patients.

10 11 **Strengths and limitations**

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14 ➤ To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
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17 ➤ This systematic review was composed of 22 studies, with 137699 gout patients.
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20 ➤ A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
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23 ➤ EMBASE database and Cochrane database library were not searched due to lack of access.
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26 ➤ Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

27 **KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis

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INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide¹. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes². Previous studies have reported that effective ULT to reduce SU levels sufficiently to prevent further crystal formation and to dissolve existing urate crystals, thus eliminating the causative agent, making gout the only chronic arthritis that can be “cured”³⁻⁵. Therefore, lifelong ULT prescription, the key to successful long-term management of gout⁶, is usually advised. But the prospect of lifelong therapy may contribute to very low adherence rate⁷. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment⁸. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies⁹. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

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7 To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for
8 different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.
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10 11 **METHODS**

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14 The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses
15 (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as closely as possible^{10,11}.
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18 19 **Search strategy**

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21 The systematic review examined the English-language databases of PubMed and Web of Science, and Chinese databases of the CNKI Scholar
22 and WanFang databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists
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24 were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles
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26 and to test the search strategy.
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32 Different search strategies were combined, as follows. For the English-language databases, search details were (adherence [All Fields] OR
33 (“patient compliance” [MeSH Terms] OR (“patient” [All Fields] AND “compliance” [All Fields]) OR “patient compliance” [All Fields] OR
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35 “compliance” [All Fields] OR “compliance” [MeSH Terms])) AND (urate-lowering [All Fields] AND (“therapy” [Subheading] OR “therapy”
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7 [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“gout” [MeSH Terms] OR “gout” [All Fields])) (see
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10 Additional file 1). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence
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12 and ULT. References of selected articles were also searched to identify additional reports.
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14 15 **Inclusion and exclusion criteria**

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17 Inclusion criteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the
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19 articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.
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22 Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to
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24 search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints,
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26 diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used
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28 the term “adherence,” but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout
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30 could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication); (7)
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32 papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of
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34 compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).
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Data extraction and quality assessment

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not meet the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: year, sample size, population, country, average age of participants, percentage of male participants, mean disease duration, type of medication, outcome, criteria for detection of adherence/compliance, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly evaluation method was used to carry out analysis. All the methods were used for subgroup analysis if not in the same subgroup. The methodological quality of each study included in the present meta-analysis was assessed using a modified version of the Newcastle-Ottawa Scale¹². Studies were judged to be at low risk of bias (≥ 3 points) or high risk of bias (< 3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

Outcome measures

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7 The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days
8 covered (PDC)], pill count, self-report or interview.
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10 11 **Statistical analysis**

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14 Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study
15 heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients¹³. Between-study
16 heterogeneity was assessed by the I^2 with thresholds of $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$ indicating low, moderate and high heterogeneity, respectively¹⁴.
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20 The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses.
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23 Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources,
24 representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and
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Egger's test were combined to explore the potential publication bias in this meta-analysis^{15, 16}. Regression analysis was performed to test the
difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The
statistical significance level was 0.05, except for the test of between-study heterogeneity.

37 **RESULTS**

Study selection

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

Study characteristics

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims¹⁷⁻³¹, with the cutpoint of $\geq 80\%$. One used prescription claim and self report³², one article used pill count³³; two used self-report^{34, 35} and three articles assessed by interview³⁶⁻³⁸. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points³⁴, 13 received 4 points^{17-21, 24-31}, 1 received 3 points²², 5 received 2 points^{23, 32, 33, 36, 37}, and 2 received 1 point^{35, 38}.

Table 1A. Baseline characteristics.

Studies	N (total)	N (ULT)	Population, Country	Age, Yrs, Mean (SD)	Male,(%)	Disease Duration,Yrs,	Medications	Quality
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							Mean (SD)		
Prescription claims									
Sarawate et al, 2006	5942	2405	Managed care database, USA	57.4(14.1)*	76.4*	NS	allopurinol	4	
Briesacher et al, 2008		9715	MEDSTAT database, USA	58.7(0.14)	77.5	NS	allopurinol, uricosurics	4	
Harrold et al, 2009		4166	Integrated delivery Systems, USA	62 (14)	75	NS	allopurinol, probenecid, sulfinpyrazone	4	
Halpern et al, 2009	18243	10070	Claims database, USA	Mean 53.9	84.2	NS	allopurinol	4	
Rashid et al, 2012		9288	KPSC health care, USA	Mean 60	78	NS	allopurinol	4	
Horsburgh et al, 2014	27,243	732	Community pharmacy dispensing databases, New Zealand	NA	39.5 †	NS	allopurinol	4	
Singh, 2014		43	Outpatient clinic, USA	63.9 (9.9)	67	NS	allopurinol, febuxostat	2	
McGowan et al, 2016	34634	15908	HSE-PCRS scheme database, Ireland	Mean 65.2*	73*	NS	allopurinol, febuxostat, probenecid,	3	

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							sulfinpyrazone	
Tan et al, 2016	91	Hospital clinics, Singapore	53.5(16.9)	92.3	NS	allopurinol, probenecid	2	
Solomon et al, 2008	9823	Medicare and PACE enrollees, USA	Mean 79	28 †	NS	allopurinol	4	
Park et al. 2012	352	242	Scott & White Health Plan, USA	61.02(15.33)*	72.4* †	NS	allopurinol, febuxostat, probenecid	4
Zandman-Goddard et al, 2013	7644	MHS database, Israel	NA	72	NS	allopurinol	4	
Mantarro et al, 2015	3727	HSD database, Italy	Mean 65	80	NS	allopurinol	4	
Rashid et al, 2015	8288	Clinical and administrative databases, USA	NA	79.80	NS	allopurinol, febuxostat, probenecid	4	
Kuo et al, 2015	49395	GPRD database, UK	NA	NA	NS	ULT	4	
Riedel et al, 2004	9482	5597	IPA plans, USA	51(11)*	82.1*	NS	allopurinol	4
Pill counts								
Lee et al, 2016	132	Outpatient clinic, Korea	51.9 (10.4)	100	100.0(89.1) [§]	allopurinol, febuxostat	2	

Self-report

Silva et al, 2010	34		Outpatient, Spain	57.1(11.8)	94.1 †	NS	allopurinol, benzbromarone	1
			People visiting the Gout and Uric Acid Education Society's website,					
Singh et al, 2016	499	251	USA	56.3(12.6)*	73.7*	NS	allopurinol, febuxostat	5

Interview

Martini et al, 2012	60	56	Community pharmacies, New Zealand	Mean 61*	90*	NS	allopurinol	2
Sheng et al, 2014	161	80 †	Gout Clinic, China	NA	NA	NS	ULD	1
van Onna et al, 2015	15	12	Outpatient clinic and primary care practices, The Netherlands	63(12)*	93.3* †	11(7)*	ULT	2

*data for total population; †Calculated based on data provided in the article. §disease duration(months)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

Table 1B. Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

Studies	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence %
Prescription claims				
Sarawate et al, 2006	compliance	MPR was calculated as medication supply actually received divided by medication supply that could have been received.	MPR \geq 80 %	28
Briesacher et al, 2008	adherence	MPR defined as the days' supply of the drug dispensed during the follow-up year divided by the number of days in the year.	MPR \geq 80 %	36.8
Harrold et al, 2009	adherence	MPR defined as the days supply of medication dispensed during the follow-up year divided by the number of days in the year and is a reliable measure of adherence.	MPR \geq 80 %	44
Halpern et al, 2009	compliance	MPR: sum of days supply from first observed allopurinol fill during the 2-year	MPR \geq 80 %	44

		observation period]/[number of days between the first observed fill and the end of		
		the post-index period.		
Rashid et al, 2012	adherence	Adherence was measured using the MPR over the follow up time period.	MPR >80 %	47.5†
Horsburgh et al, 2014	adherence	MPR defined as the ratio of days supplied from initial dispensing to the number of days to the end of the study period or the patient's date of death.	MPR ≥80 %	78†
Singh, 2014	adherence	Self-report adherence to ULT.	MPR ≥0.80	32.6†
McGowan et al, 2016	adherence	MPR defined as the number of doses filled by the pharmacist divided by the number of days in the defined period (6 or 12 months).	MPR ≥80 %	45.5
Tan et al, 2016	adherence	MPR summarized the proportion of days a patient has a supply of medications for.	MPR ≥80 %	83.5
Solomon et al, 2008	adherence	PDC was calculated as the days with available UALT divided by the total number of days of follow-up.	PDC ≥ 80%	36†
Park et al. 2012	adherence	PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand.	PDC ≥ 80%	26.9†

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		Mean PDC calculated by dividing the quantity of allopurinol dispensed by the total		
Zandman-Goddard et al, 2013	adherence	time interval from index date to drug cessation, death, leaving MHS or 31 December 2009, whichever occurred first.	PDC \geq 80%	17
Mantarro et al, 2015	adherence	PDC defined as dividing the cumulative days of medication use by the length of follow up.	PDC \geq 80%	45.9
Rashid et al, 2015	adherence	PDC was defined as the number of days with ULT drug dispensed divided by the number of days in the specified time interval (365 days).	PDC \geq 80%	48.2†
Kuo et al, 2015	adherence	PDC defined as the period from the latest of registration date or 1 January to the earliest of transfer-out, death date or 31 December of the calendar year specified.	PDC \geq 80%	39.66
Riedel et al, 2004	compliance	Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc	Compliance rate \geq 80%	18
Pill count				
Lee et al, 2016	compliance	Pill counts: noncompliance was defined as <80% of the prescribed dose taken.	Pill count \geq 80%	71.2

Self-report

10	Silva et al, 2010	compliance	Compliance defined as taking medication regularly, as prescribed.	NS	53 [†]
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12	Singh et al, 2016	adherence	Number of days the patient forgot to take ULT in the last month.	Adherence >0.80	78.5
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14				MMAS-8 score ≥ 6	
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16	Tan et al, 2016	adherence	MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8)		61.9
17				(75%)	
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23	Martini et al, 2012	compliance	Participants admitted to not taking ULTs as prescribed.	NS	79
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26	Sheng et al, 2014	adherence	Adherence was defined as sustained use of ULD in the prior 12 months, otherwise	NS	53.8 [†]
27			non-adherence.		
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30	van Onna et al, 2015	adherence	Non-adherence at some point in time was defined as admission in the interview.	NS	50.0 [†]

[†]Calculated based on data provided in the article.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky

Medication Adherence Scale; NS: not stated

The rate of adherence to ULT among gout patients.

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2 = 99.7%$) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2 = 86.3%$) for self-report and 63% (95% CI, 42%-83%, $I^2 = 82.9%$) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P = 0.535$).

Sensitivity and subgroup analyses

Sensitivity analysis indicated that all of the estimated values were in regions of the lower CI limit and upper CI limit, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality. The results of the meta-analysis affected by the country of origin in those included studies, showed that studies from the Oceania had higher adherence estimates [78% (95% CI, 75%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

Table 2. Summary of adherence rate and heterogeneity findings.

Outcomes	No. of studies	No. of participants	Adherence, % (95%	Heterogeneity		Test for overall effect	
			confidence intervals)	<i>P</i> -value	<i>I</i> ² (%)	<i>Z</i>	<i>P</i> -value
Overall	22	137699	47(42, 52)	0.000	99.7	18.66	0.000
Measurement methods							
Prescription claims	16	137134	42(37, 47)	0.000	99.8	15.61	0.000
Pill count	1	132	71(63, 79)	-	-	18.06	0.000
Self-report	3	376	66(50, 81)	0.001	86.3	8.40	0.000
Interview	3	148	63(42,83)	0.003	82.9	6.09	0.000
Publication Year							
2010s	6	41766	34(26, 43)	0.000	99.7	8.22	0.000

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2010-	16	95923	53(47, 60)	0.000	99.7	15.95	0.000
Country of origin							
America	11	59888	40(33, 47)	0.000	99.6	11.82	0.000
Oceania	2	788	78(75, 81)	0.860	0	52.97	0.000
Europe	5	69076	44(40, 49)	0.000	98.0	19.62	0.000
Asia	4	7947	56(17, 96)	0.000	99.4	2.81	0.000
Data sources							
Database	14	13700	40(34, 45)	0.000	99.8	13.48	0.000
Non-database	8	699	65(54, 75)	0.000	89.2	11.81	0.000
Representativeness							
Multiple sites	17	137319	44(39, 50)	0.000	99.8	15.79	0.000
A single site	5	380	60(43, 76)	0.000	92.1	7.04	0.000
Sample size							

≥ 200	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
< 200	7	448	62(48, 75)	0.000	89.3	9.12	0.000
Cutpoint							
≥80%	18	137517	45(40, 51)	0.000	99.7	16.70	0.000
≥75%	1	19	62(52, 72)	0.004	77.8	7.54	0.000
NS	4	182	60(45, 76)	-	-	12.16	0.000
Quality							
≥3 points	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
<3points	7	448	62(48, 75)	0.000	89.3	9.12	0.000

Publication bias

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), $P = 0.356$; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

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7 $P = 0.664$; Egger: bias = -4.92 (95% CI: $-20.50, 10.66$), $P = 0.155$; Egger: bias = -2.02 (95% CI: $-70.13, 66.08$), $P = 0.770$, respectively] (Figure
8 not shown).
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10 11 **DISCUSSION**

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14 To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence
15 and to seek a relationship between adherence and the method used to measure it.
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19 Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were
20 presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview,
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22 respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, self-report, interview,
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24 and prescription claims. Although no statistical differences were found among the different methods, suboptimal medication adherence was clear
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26 across the included studies. It is particularly shocking that the adherence rate of 42% based on prescription claims and the overall adherence rate
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28 of 47% are below the well-quoted WHO estimate that 50% of adults adhere to long-term therapies.
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35 A previous systematic review included 16 studies⁹. We identified an additional studies. Importantly, the previous review did not quantify
36 adherence. In our meta-analysis, most studies used a cutpoint of $\geq 80\%$ to define adherent patients. Data on persistence, discontinuation,
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7 switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.
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10 The results demonstrated an overall adherence rate to ULT in adult gout patients of 47%. However, heterogeneity was large. By subgroup
11 analysis for measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and
12 overall quality in those included studies, country of origin was found to contributed to the heterogeneity between studies, with heterogeneity of
13 0% among studies from Oceania, 99.6% from America, 98.0% from Europe, and 99.4% from Asia. Although studies varied widely in terms of
14 quality, our sensitivity analyses suggested that adherence rate estimates were reasonably stable.
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22 This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from UK. The
23 reasons for this could be that interview studies or postal surveys are prompting patients to self-report higher adherence. Additionally, adherence
24 also depends on the healthcare system in which the study is done - private (with billing for drugs used) vs. government funded; primary care vs.
25 secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the
26 findings.
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35 Because of the low adherence with ULT, it is particularly important to carry out potential interventions to achieve improved gout-related
36 outcomes. These interventions include initiation of prophylactic anti-inflammatory medication when starting ULT, frequent follow-ups, regular
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7 serum urate monitoring and improved patient education, which can be achieved through pharmacist- or nurse-assisted programs³⁹. Abhishek
8 Abhishek et al⁴⁰ and Rees et al⁴¹ have confirmed that there are excellent adherence rates after nurse led treatment of gout, which means that
9 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.
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15 There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed.
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17 First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as
18 gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access,
19 our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified
20 ULT were excluded, which could bias the findings.
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27 **CONCLUSION**

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30 The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more
31 attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout
32 patients.
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9 **Competing interests**

10 The authors declared that they have no competing interests.
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26

27 **Authors' contributions**

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30 RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality,
31
32 analyzed the data and wrote the draft of the paper. GZ, YC, LZ, QZ, TF, HC, LL, and ZG gave advice on meta-analysis methodology and revised
33
34 the paper. All authors contributed to reviewing or revising the paper. LL and ZG were the guarantors of this work and had full access to all the
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36 data in the study and took responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final
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10 **Ethics approval and consent to participate**

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12 Ethical approval and consent to participate are not required for this review.

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7 **Figure 1.** Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15
8 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were
9 excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies
10 were included in the quantitative synthesis (meta-analysis).
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15 **Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.
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18 **Additional file 1:** Search strategy.
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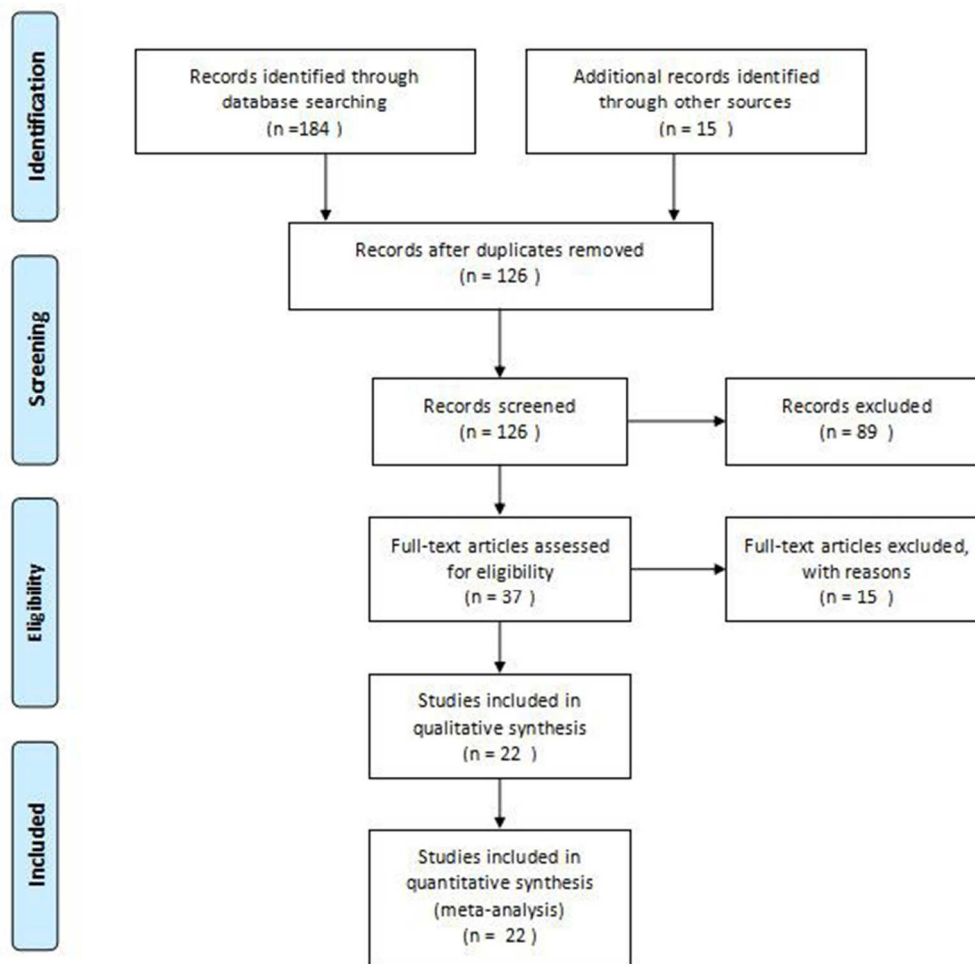


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

49x48mm (300 x 300 DPI)

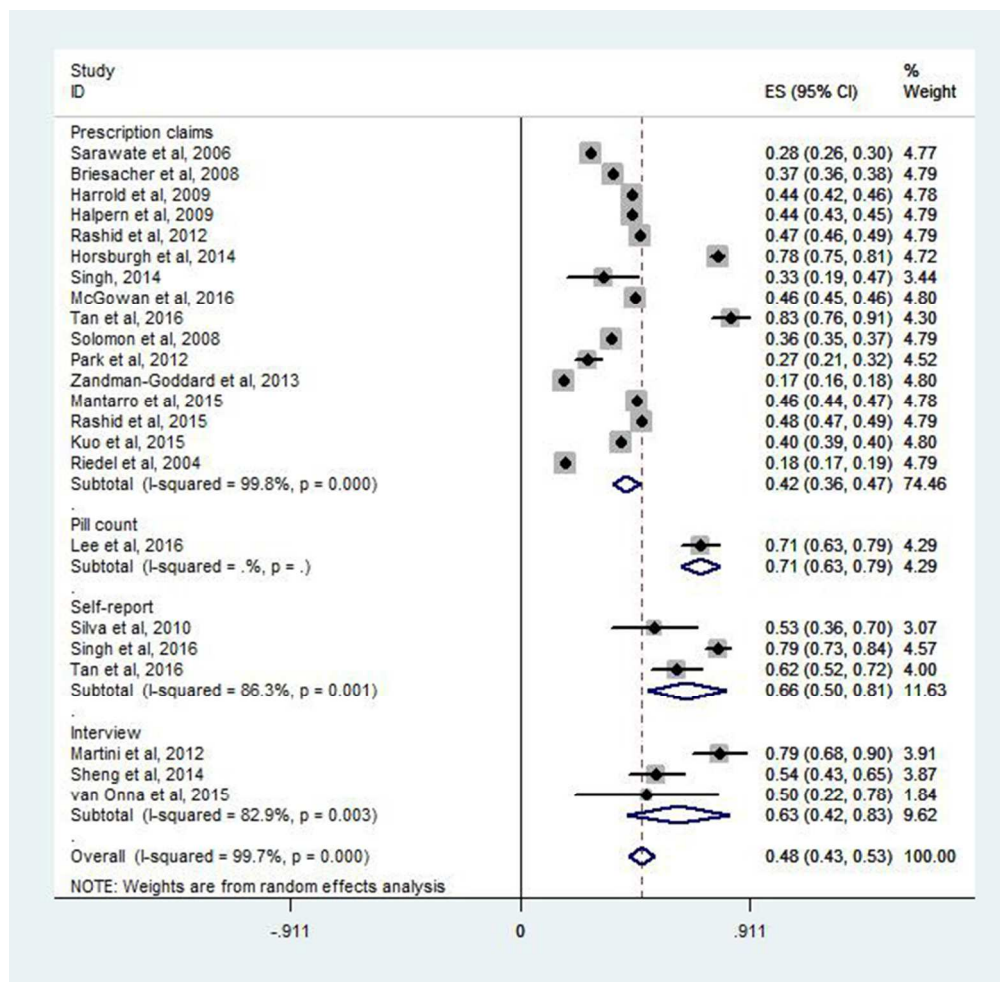


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

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Additional file 1: Search strategy

PubMed/Web of Science:

(adherence OR compliance) AND urate-lowering therapy AND gout

For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NO
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NO
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NO
Support:			
Sources	5a	Indicate sources of financial or other support for the review	24
Sponsor	5b	Provide name for the review funder and/or sponsor	NO
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NO
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9-17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	17-20
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NO
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20-21
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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Keywords:	adherence, urate-lowering therapy, gout, meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

ABSTRACT

Introduction Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

Methods The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

Results A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2 = 99.7%$). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2=86.3%$) for self-report, and 63% (95% CI, 42%-83%, $I^2 = 82.9%$) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

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7 **Conclusions** Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay
8 more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult
9 gout patients.
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14 **Strengths and limitations**

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17 ➤ To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
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19 ➤ This systematic review was composed of 22 studies, with 137699 gout patients.
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21 ➤ A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
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23 ➤ EMBASE database and Cochrane database library were not searched due to lack of access.
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25 ➤ Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.
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30 **KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis
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INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide¹. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes². Previous studies have reported that effective ULT to reduce SU levels sufficiently to prevent further crystal formation and to dissolve existing urate crystals, thus eliminating the causative agent, making gout the only chronic arthritis that can be “cured”³⁻⁵. Therefore, lifelong ULT prescription, the key to successful long-term management of gout⁶, is usually advised. But the prospect of lifelong therapy may contribute to very low adherence rate⁷. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment⁸. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies⁹. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

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7 To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for
8 different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.
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10 11 **METHODS**

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14 The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses
15 (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as closely as possible^{10,11}.
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18 19 **Search strategy**

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21 The systematic review examined the English-language databases of PubMed and Web of Science, and Chinese databases of the CNKI Scholar
22 and WanFang databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists
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24 were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles
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26 and to test the search strategy.
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32 Different search strategies were combined, as follows. For the English-language databases, search details were (adherence [All Fields] OR
33 (“patient compliance” [MeSH Terms] OR (“patient” [All Fields] AND “compliance” [All Fields]) OR “patient compliance” [All Fields] OR
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35 “compliance” [All Fields] OR “compliance” [MeSH Terms])) AND (urate-lowering [All Fields] AND (“therapy” [Subheading] OR “therapy”
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7 [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“gout” [MeSH Terms] OR “gout” [All Fields])) (see
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10 Additional file 1). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence
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12 and ULT. References of selected articles were also searched to identify additional reports.
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14 15 **Inclusion and exclusion criteria**

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17 Inclusion criteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the
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19 articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.
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22 Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to
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24 search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints,
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26 diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used
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28 the term “adherence,” but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout
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30 could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication); (7)
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32 papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of
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34 compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).
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Data extraction and quality assessment

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not meet the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: year, sample size, population, country, average age of participants, percentage of male participants, mean disease duration, type of medication, outcome, criteria for detection of adherence/compliance, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly evaluation method was used to carry out analysis. All the methods were used for subgroup analysis if not in the same subgroup. The methodological quality of each study included in the present meta-analysis was assessed using a modified version of the Newcastle-Ottawa Scale¹². Studies were judged to be at low risk of bias (≥ 3 points) or high risk of bias (< 3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

Outcome measures

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7 The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days
8 covered (PDC)], pill count, self-report or interview.
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10 11 **Statistical analysis**

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14 Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study
15 heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients¹³. Between-study
16 heterogeneity was assessed by the I^2 with thresholds of $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$ indicating low, moderate and high heterogeneity, respectively¹⁴.
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20 The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses.
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23 Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources,
24 representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and
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30 Egger's test were combined to explore the potential publication bias in this meta-analysis^{15, 16}. Regression analysis was performed to test the
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36 difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The
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49 statistical significance level was 0.05, except for the test of between-study heterogeneity.

37 **RESULTS**

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Study selection

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

Study characteristics

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims¹⁷⁻³¹, with the cutpoint of ≥80%. One used prescription claim and self report³², one article used pill count³³; two used self-report^{34, 35} and three articles assessed by interview³⁶⁻³⁸. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points³⁴, 13 received 4 points^{17-21, 24-31}, 1 received 3 points²², 5 received 2 points^{23, 32, 33, 36, 37}, and 2 received 1 point^{35, 38}.

Table 1A. Baseline characteristics.

Studies	N (total)	N (ULT)	Population, Country	Age, Yrs, Mean (SD)	Male,(%)	Disease Duration,Yrs,	Medications	Quality
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								Mean (SD)	
Prescription claims									
Sarawate et al, 2006	5942	2405	Managed care database, USA	57.4(14.1)*	76.4*	NS	allopurinol		4
Briesacher et al, 2008		9715	MEDSTAT database, USA	58.7(0.14)	77.5	NS	allopurinol, uricosurics		4
Harrold et al, 2009		4166	Integrated delivery Systems, USA	62 (14)	75	NS	allopurinol, probenecid, sulfinpyrazone		4
Halpern et al, 2009	18243	10070	Claims database, USA	Mean 53.9	84.2	NS	allopurinol		4
Rashid et al, 2012		9288	KPSC health care, USA	Mean 60	78	NS	allopurinol		4
Horsburgh et al, 2014	27,243	732	Community pharmacy dispensing databases, New Zealand	NA	39.5 †	NS	allopurinol		4
Singh, 2014		43	Outpatient clinic, USA	63.9 (9.9)	67	NS	allopurinol, febuxostat		2
McGowan et al, 2016	34634	15908	HSE-PCRS scheme database, Ireland	Mean 65.2*	73*	NS	allopurinol, febuxostat, probenecid,		3

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							sulfinpyrazone	
Tan et al, 2016	91	Hospital clinics, Singapore	53.5(16.9)	92.3	NS	allopurinol, probenecid	2	
Solomon et al, 2008	9823	Medicare and PACE enrollees, USA	Mean 79	28 †	NS	allopurinol	4	
Park et al. 2012	352	242	Scott & White Health Plan, USA	61.02(15.33)*	72.4* †	NS	allopurinol, febuxostat, probenecid	4
Zandman-Goddard et al, 2013	7644	MHS database, Israel	NA	72	NS	allopurinol	4	
Mantarro et al, 2015	3727	HSD database, Italy	Mean 65	80	NS	allopurinol	4	
Rashid et al, 2015	8288	Clinical and administrative databases, USA	NA	79.80	NS	allopurinol, febuxostat, probenecid	4	
Kuo et al, 2015	49395	GPRD database, UK	NA	NA	NS	ULT	4	
Riedel et al, 2004	9482	5597	IPA plans, USA	51(11)*	82.1*	NS	allopurinol	4
Pill counts								
Lee et al, 2016	132	Outpatient clinic, Korea	51.9 (10.4)	100	100.0(89.1) [§]	allopurinol, febuxostat	2	

Self-report

Silva et al, 2010	34		Outpatient, Spain	57.1(11.8)	94.1 †	NS	allopurinol, benzbromarone	1
			People visiting the Gout and Uric Acid Education Society's website,					
Singh et al, 2016	499	251	USA	56.3(12.6)*	73.7*	NS	allopurinol, febuxostat	5
Interview								
Martini et al, 2012	60	56	Community pharmacies, New Zealand	Mean 61*	90*	NS	allopurinol	2
Sheng et al, 2014	161	80 †	Gout Clinic, China	NA	NA	NS	ULD	1
van Onna et al, 2015	15	12	Outpatient clinic and primary care practices, The Netherlands	63(12)*	93.3* †	11(7)*	ULT	2

*data for total population; †Calculated based on data provided in the article. §disease duration(months)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

Table 1B. Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

Studies	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence %
Prescription claims				
Sarawate et al, 2006	compliance	MPR was calculated as medication supply actually received divided by medication supply that could have been received.	MPR \geq 80 %	28
Briesacher et al, 2008	adherence	MPR defined as the days' supply of the drug dispensed during the follow-up year divided by the number of days in the year.	MPR \geq 80 %	36.8
Harrold et al, 2009	adherence	MPR defined as the days supply of medication dispensed during the follow-up year divided by the number of days in the year and is a reliable measure of adherence.	MPR \geq 80 %	44
Halpern et al, 2009	compliance	MPR: sum of days supply from first observed allopurinol fill during the 2-year	MPR \geq 80 %	44

		observation period]/[number of days between the first observed fill and the end of		
		the post-index period.		
Rashid et al, 2012	adherence	Adherence was measured using the MPR over the follow up time period.	MPR >80 %	47.5†
Horsburgh et al, 2014	adherence	MPR defined as the ratio of days supplied from initial dispensing to the number of days to the end of the study period or the patient's date of death.	MPR ≥80 %	78†
Singh, 2014	adherence	Self-report adherence to ULT.	MPR ≥0.80	32.6†
McGowan et al, 2016	adherence	MPR defined as the number of doses filled by the pharmacist divided by the number of days in the defined period (6 or 12 months).	MPR ≥80 %	45.5
Tan et al, 2016	adherence	MPR summarized the proportion of days a patient has a supply of medications for.	MPR ≥80 %	83.5
Solomon et al, 2008	adherence	PDC was calculated as the days with available UALT divided by the total number of days of follow-up.	PDC ≥ 80%	36†
Park et al. 2012	adherence	PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand.	PDC ≥ 80%	26.9†

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		Mean PDC calculated by dividing the quantity of allopurinol dispensed by the total		
Zandman-Goddard et al, 2013	adherence	time interval from index date to drug cessation, death, leaving MHS or 31 December 2009, whichever occurred first.	PDC \geq 80%	17
Mantarro et al, 2015	adherence	PDC defined as dividing the cumulative days of medication use by the length of follow up.	PDC \geq 80%	45.9
Rashid et al, 2015	adherence	PDC was defined as the number of days with ULT drug dispensed divided by the number of days in the specified time interval (365 days).	PDC \geq 80%	48.2†
Kuo et al, 2015	adherence	PDC defined as the period from the latest of registration date or 1 January to the earliest of transfer-out, death date or 31 December of the calendar year specified.	PDC \geq 80%	39.66
Riedel et al, 2004	compliance	Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc	Compliance rate \geq 80%	18
Pill count				
Lee et al, 2016	compliance	Pill counts: noncompliance was defined as <80% of the prescribed dose taken.	Pill count \geq 80%	71.2

Self-report

10	Silva et al, 2010	compliance	Compliance defined as taking medication regularly, as prescribed.	NS	53 [†]
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12	Singh et al, 2016	adherence	Number of days the patient forgot to take ULT in the last month.	Adherence >0.80	78.5
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16	Tan et al, 2016	adherence	MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8)	MMAS-8 score \geq 6	61.9
17				(75%)	
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23	Martini et al, 2012	compliance	Participants admitted to not taking ULTs as prescribed.	NS	79
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26	Sheng et al, 2014	adherence	Adherence was defined as sustained use of ULD in the prior 12 months, otherwise	NS	53.8 [†]
27			non-adherence.		
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30	van Onna et al, 2015	adherence	Non-adherence at some point in time was defined as admission in the interview.	NS	50.0 [†]

[†]Calculated based on data provided in the article.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky

Medication Adherence Scale; NS: not stated

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The rate of adherence to ULT among gout patients.

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2 = 99.7%$) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2 = 99.8%$) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2 = 86.3%$) for self-report and 63% (95% CI, 42%-83%, $I^2 = 82.9%$) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P = 0.535$).

Sensitivity and subgroup analyses

Sensitivity analysis indicated that all of the estimated values were in regions of the lower CI limit and upper CI limit, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality. The results of the meta-analysis affected by the country of origin in those included studies, showed that studies from the Oceania had higher adherence estimates [78% (95% CI, 75%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

Table 2. Summary of adherence rate and heterogeneity findings.

Outcomes	No. of studies	No. of participants	Adherence, % (95%	Heterogeneity		Test for overall effect	
			confidence intervals)	<i>P</i> -value	<i>I</i> ² (%)	<i>Z</i>	<i>P</i> -value
Overall	22	137699	47(42, 52)	0.000	99.7	18.66	0.000
Measurement methods							
Prescription claims	16	137134	42(37, 47)	0.000	99.8	15.61	0.000
Pill count	1	132	71(63, 79)	-	-	18.06	0.000
Self-report	3	376	66(50, 81)	0.001	86.3	8.40	0.000
Interview	3	148	63(42,83)	0.003	82.9	6.09	0.000
Publication Year							
2010s	6	41766	34(26, 43)	0.000	99.7	8.22	0.000

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2010-	16	95923	53(47, 60)	0.000	99.7	15.95	0.000
Country of origin							
America	11	59888	40(33, 47)	0.000	99.6	11.82	0.000
Oceania	2	788	78(75, 81)	0.860	0	52.97	0.000
Europe	5	69076	44(40, 49)	0.000	98.0	19.62	0.000
Asia	4	7947	56(17, 96)	0.000	99.4	2.81	0.000
Data sources							
Database	14	13700	40(34, 45)	0.000	99.8	13.48	0.000
Non-database	8	699	65(54, 75)	0.000	89.2	11.81	0.000
Representativeness							
Multiple sites	17	137319	44(39, 50)	0.000	99.8	15.79	0.000
A single site	5	380	60(43, 76)	0.000	92.1	7.04	0.000
Sample size							

≥ 200	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
< 200	7	448	62(48, 75)	0.000	89.3	9.12	0.000
Cutpoint							
≥80%	18	137517	45(40, 51)	0.000	99.7	16.70	0.000
≥75%	1	19	62(52, 72)	0.004	77.8	7.54	0.000
NS	4	182	60(45, 76)	-	-	12.16	0.000
Quality							
≥3 points	15	137251	42(36, 48)	0.000	99.8	14.55	0.000
<3points	7	448	62(48, 75)	0.000	89.3	9.12	0.000

Publication bias

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), $P = 0.356$; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

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7 $P = 0.664$; Egger: bias = -4.92 (95% CI: $-20.50, 10.66$), $P = 0.155$; Egger: bias = -2.02 (95% CI: $-70.13, 66.08$), $P = 0.770$, respectively] (Figure
8 not shown).
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10 11 **DISCUSSION**

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14 To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence
15 and to seek a relationship between adherence and the method used to measure it.
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19 Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were
20 presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview,
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22 respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, self-report, interview,
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24 and prescription claims. Although no statistical differences were found among the different methods, suboptimal medication adherence was clear
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26 across the included studies. It is particularly shocking that the adherence rate of 42% based on prescription claims and the overall adherence rate
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28 of 47% are below the well-quoted WHO estimate that 50% of adults adhere to long-term therapies.
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35 A previous systematic review included 16 studies⁹. We identified an additional studies. Importantly, the previous review did not quantify
36 adherence. In our meta-analysis, most studies used a cutpoint of $\geq 80\%$ to define adherent patients. Data on persistence, discontinuation,
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7 switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.
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10 The results demonstrated an overall adherence rate to ULT in adult gout patients of 47%. However, heterogeneity was large. By subgroup
11 analysis for measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and
12 overall quality in those included studies, country of origin was found to contributed to the heterogeneity between studies, with heterogeneity of
13 0% among studies from Oceania, 99.6% from America, 98.0% from Europe, and 99.4% from Asia. Although studies varied widely in terms of
14 quality, our sensitivity analyses suggested that adherence rate estimates were reasonably stable.
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22 This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from UK. The
23 reasons for this could be that interview studies or postal surveys are prompting patients to self-report higher adherence. Additionally, adherence
24 also depends on the healthcare system in which the study is done - private (with billing for drugs used) vs. government funded; primary care vs.
25 secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the
26 findings.
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35 The adherence rate is surprisingly low considering ULT does not have significant side effects or require taking tablets several times a day. It
36 could be that patients don't think it is necessary to always take urate-lowering agents (ULA) since they may feel asymptomatic most of the time.
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7 It could also be that ULA are not included in the medical insurance, while the price is higher, long-term use of ULA will cause a greater financial
8 burden on gout patients.
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11 Because of the low adherence with ULT, it is particularly important to carry out potential interventions to achieve improved gout-related
12 outcomes. These interventions include initiation of prophylactic anti-inflammatory medication when starting ULT, frequent follow-ups, regular
13 serum urate monitoring and improved patient education, which can be achieved through pharmacist- or nurse-assisted programs³⁹. Abhishek
14 Abhishek et al⁴⁰ and Rees et al⁴¹ have confirmed that there are excellent adherence rates after nurse led treatment of gout, which means that
15 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.
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25 There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed.
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27 First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as
28 gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access,
29 our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified
30 ULT were excluded, which could bias the findings.
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37 CONCLUSION

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7 The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more
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9 attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout
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11 patients.
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20 **Competing interests**

21
22 The authors declared that they have no competing interests.
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33 HS2016003).
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37 **Authors' contributions**

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7 RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality,
8
9 analyzed the data and wrote the draft of the paper. GZ, YC, LZ, QZ, TF, HC, LL, and ZG gave advice on meta-analysis methodology and revised
10
11 the paper. All authors contributed to reviewing or revising the paper. LL and ZG were the guarantors of this work and had full access to all the
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13 data in the study and took responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final
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15 manuscript.
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18 19 20 **Ethics approval and consent to participate**

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22 Ethical approval and consent to participate are not required for this review.
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7 **Figure 1.** Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15
8 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were
9 excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies
10 were included in the quantitative synthesis (meta-analysis).
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15 **Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.
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18 **Additional file 1:** Search strategy.
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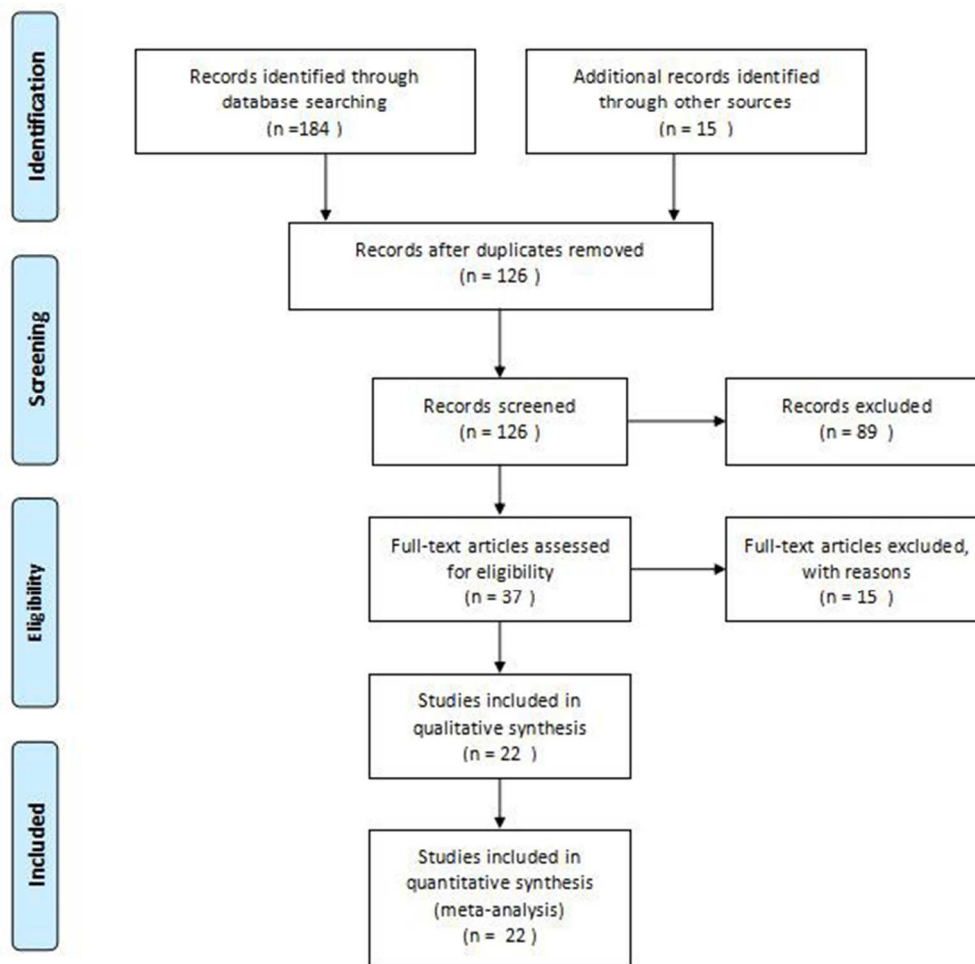


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening. Then the remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

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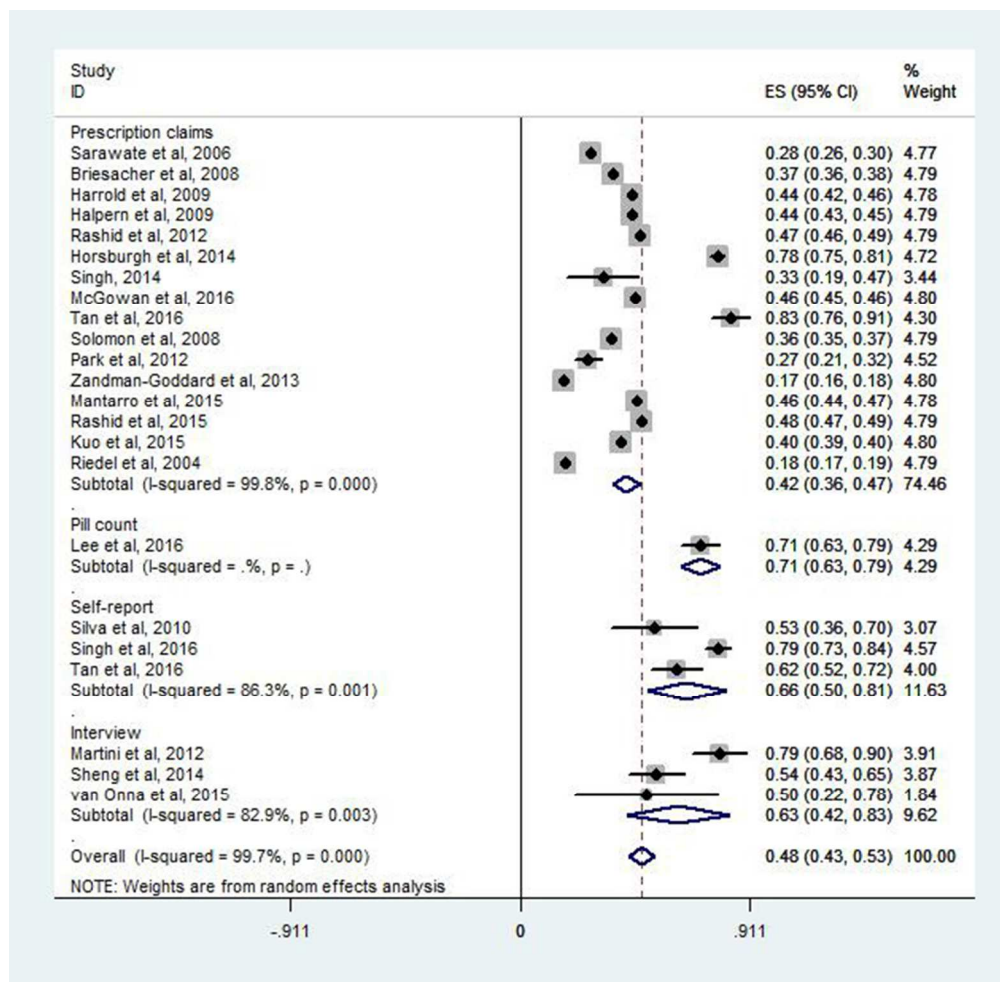


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

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Additional file 1: Search strategy

PubMed/Web of Science:

(adherence OR compliance) AND urate-lowering therapy AND gout

For peer review only



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20-21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	17-20
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

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