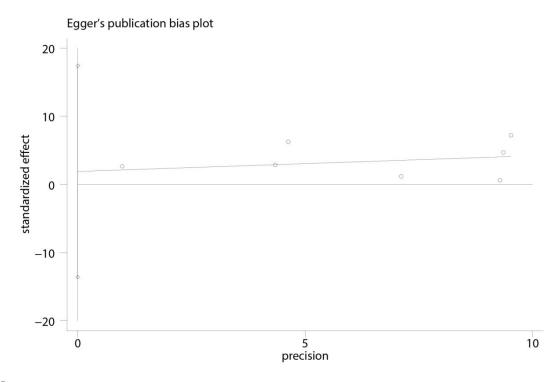
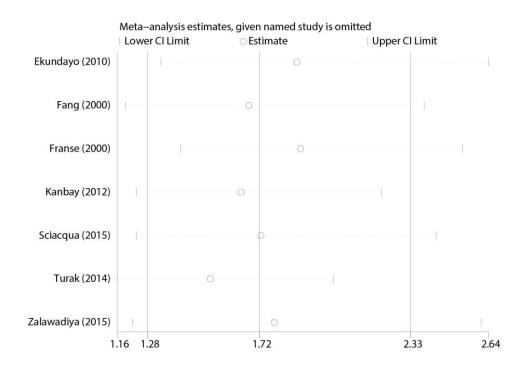
Supplementary Figure 1: Methodological quality assessment of included randomized controlled trials treating hyperuricemia and gout with urate-lowering therapies.

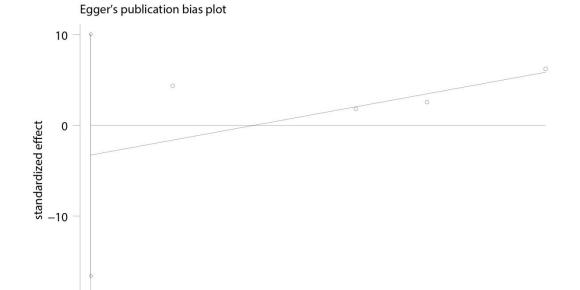
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Becker,2009	?	?	?	?	+	?	•
Becker,2010	?	?	•	•	•	?	•
Dalbeth,2017	?	?	+	•	•	?	•
Givertz,2015	•	?	•	•	•	?	•
Goicoechea,2015	?	?	•	?	•	?	•
Huang,2014	•	•	•	•	•	?	•
Jiang,2014	?	?	•	•	?	?	?
Kimura,2018	•	•	•	•	+	•	?
Lu,2016	•	?	?	?	+	?	?
Nong,2018	?	?	?	?	+	?	?
Saag,2016	•	•	+	•	•	+	?
Saag,2019	•	+	+	+	+	+	?
Schumacher,2008		?	•	•	+	?	•
Tang,2017		?	?	?	+	?	?
Tuta,2014	?	?	?	?	?	?	?
Wang,2013	?	?	•	•	+	?	•
White,2018	?	?	•	•	•	•	•

Supplementary Figure 2: Egger publication bias plot (A) and sensitivity analysis result (B) of comparison between hyperuricemia and non-hyperuricemia in MACE. Egger publication bias plot (C) and sensitivity analysis result (D) of comparison between hyperuricemia and non-hyperuricemia in CVE. CVE: Cardiovascular events; MACE: Major adverse cardiovascular events.

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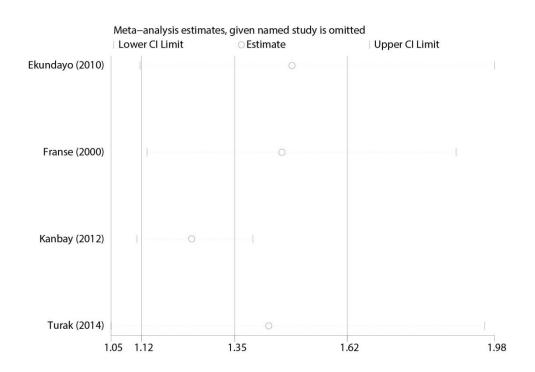




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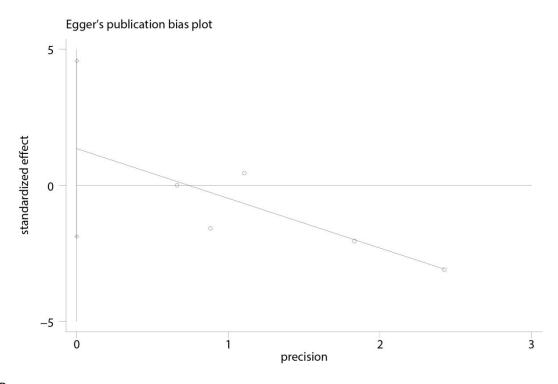
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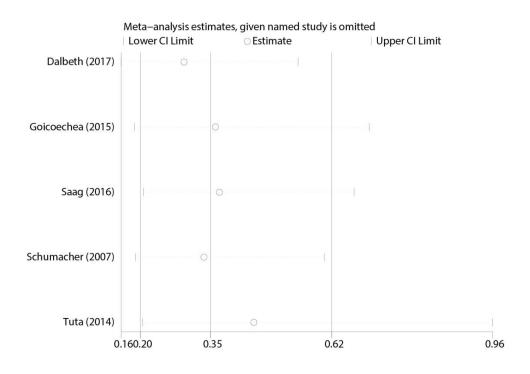
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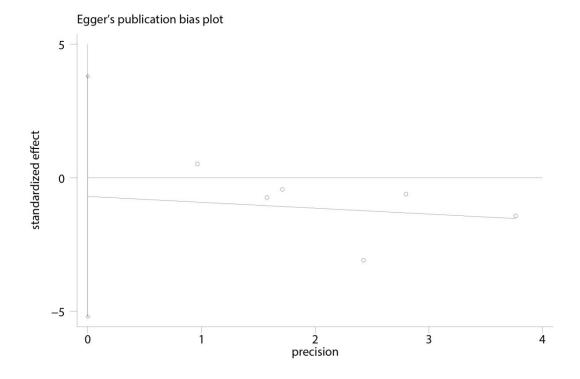
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Supplementary Figure 3: Egger publication bias plot (A) and sensitivity analysis result (B) of comparison between XOIs and non-XOIs/placebo in MACE with low CV risk. Egger publication bias plot (C) and sensitivity analysis result (D) of comparison between XOIs and non-XOIs/placebo in CVE with low CV risk. CV: Cardiovascular; CVE: Cardiovascular events; MACE: Major adverse cardiovascular events, XOIs: Xanthine oxidase inhibitors.

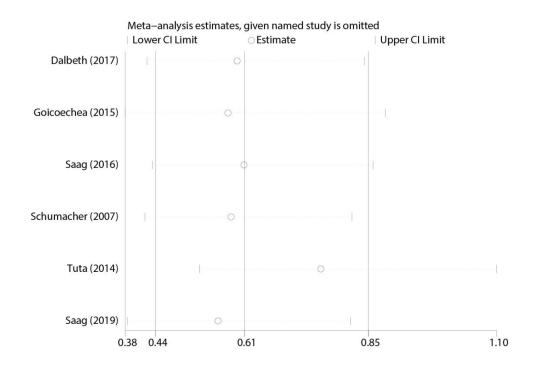
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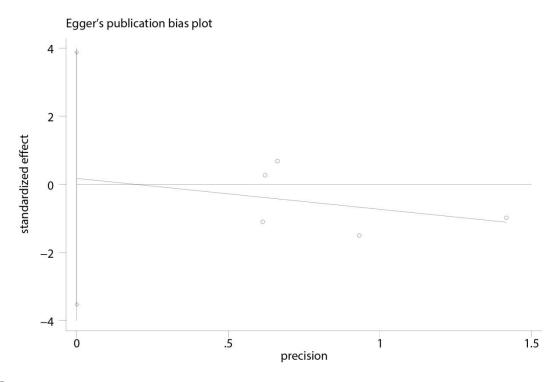


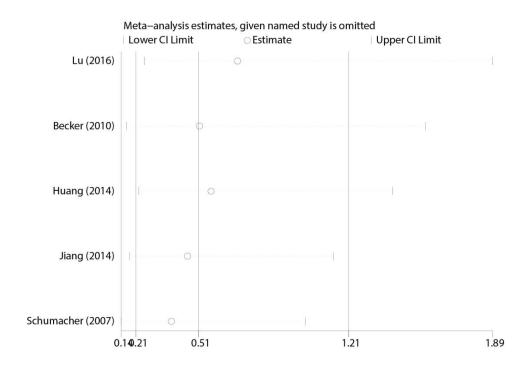
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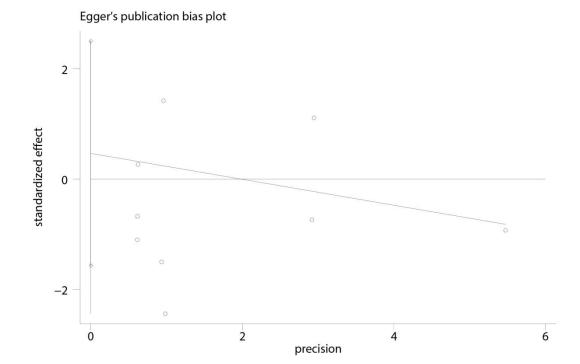


Supplementary Figure 4: Egger publication bias plot (A) and sensitivity analysis result (B) of comparison between febuxostat and allopurinol in MACE with low CV risk. Egger publication bias plot (C) and sensitivity analysis result (D) of comparison between febuxostat and allopurinol in CVE with low CV risk. CV: Cardiovascular; CVE: Cardiovascular events; MACE: Major adverse cardiovascular events.

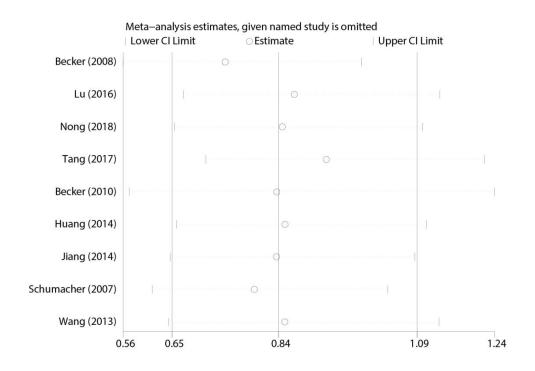
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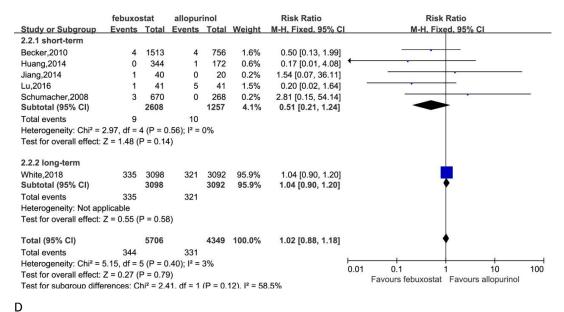


Supplementary Figure 5: Subgroup meta-analysis based on short-term (<12 m) and long-term (≥12 m) of MACE (A) and CVE (B) in comparison between XOIs and placebo. Subgroup meta-analysis based on short-term (<12 m) and long-term (≥12 m) of MACE (C) and CVE (D) in comparison between allopurinol and febuxostat. XOIs: Xanthine oxidase inhibitors; MACE: major adverse cardiovascular events, CVE: cardiovascular events.



	XOIs		no treatment or pla	cebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.3.1 short-term							* °
Givertz,2015	5	128	7	125	12.1%	0.70 [0.23, 2.14]	
Schumacher,2008	3	938	0	134	1.5%	1.01 [0.05, 19.38]	-
Subtotal (95% CI)		1066		259	13.6%	0.73 [0.26, 2.08]	
Total events	8		7				
Heterogeneity: Chi ² = 0	.05, df =	1 (P = (0.82); $I^2 = 0\%$				
Test for overall effect: 2	Z = 0.59 (F	P = 0.5	6)				
1.3.2 long-term							
Dalbeth,2017	3	82	2	76	3.5%	1.39 [0.24, 8.09]	- 11
Goicoechea,2015	4	57	12	56	20.7%	0.33 [0.11, 0.95]	-
Kimura 2018	5	219	9	222	15.3%	0.56 [0.19, 1.65]	
Saag,2016	1	64	3	32	6.8%	0.17 [0.02, 1.54]	-
Tuta,2014	6	52	26	63	40.1%	0.28 [0.12, 0.63]	
Subtotal (95% CI)		474		449	86.4%	0.38 [0.23, 0.62]	•
Total events	19		52				
Heterogeneity: Chi ² = 3	.75, df = 4	4 (P = 0	0.44); I ² = 0%				
Test for overall effect: 2	z = 3.83 (I	P = 0.0	001)				
Total (95% CI)		1540		708	100.0%	0.43 [0.27, 0.66]	•
Total events	27		59				
Heterogeneity: Chi2 = 5	.02, df = 6	6 (P = (0.54); I ² = 0%				201 01 10 100
Test for overall effect: 2	Z = 3.75 (I	0.0	002)				0.01 0.1 1 10 100
Test for subaroup differ	rences: Cl	hi² = 1.	25. df = 1 (P = 0.26).	$I^2 = 20.0$	1%		Favours XOIs Favours non-UXOIs/placebo

	XOIs		no treatment or pla	acebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events 7	Γotal	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.2.1 short-term					=		
Givertz,2015	52	128	67	125	39.3%	0.76 [0.58, 0.99]	—
Saag,2019	32	1420	10	356	9.3%	0.80 [0.40, 1.62]	
Schumacher,2008	12	938	1	134	1.0%	1.71 [0.22, 13.08]	
Subtotal (95% CI)	2	2486		615	49.6%	0.79 [0.61, 1.01]	•
Total events	96		78				
Heterogeneity: Chi ² = 0	0.64, df = 2	(P = (0.73); $I^2 = 0\%$				
Test for overall effect: 2	Z = 1.87 (P	= 0.0	6)				
1.2.2 long-term							
Dalbeth,2017	5	82	6	76	3.6%	0.77 [0.25, 2.43]	
Goicoechea,2015	16	57	23	56	13.4%	0.68 [0.41, 1.15]	-
Kimura 2018	15	219	29	222	16.7%	0.52 [0.29, 0.95]	
Saag,2016	5	64	4	32	3.1%	0.63 [0.18, 2.17]	,
Tuta,2014	6	52	26	63	13.6%	0.28 [0.12, 0.63]	 -
Subtotal (95% CI)		474		449	50.4%	0.52 [0.38, 0.73]	◆
Total events	47		88				
Heterogeneity: Chi ² = 3	3.84, df = 4	(P = ($(0.43); I^2 = 0\%$				
Test for overall effect: 2	Z = 3.89 (P	= 0.0	001)				
Total (95% CI)	2	2960		1064	100.0%	0.65 [0.53, 0.80]	•
Total events	143		166				•
Heterogeneity: Chi ² = 7	7.27. df = 7	(P = (0.40); I ² = 4%				
Test for overall effect: 2							0.01 0.1 1 10 100
Test for subgroup differ	THE RESERVE OF THE PARTY OF THE		Addition to the part of the property of the part of th	$I^2 = 72.9$	1%		Favours XOIs Favours non-XOIs/placebo



febuxostat allopurinol Risk Ratio Risk Ratio M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup Events Total Events Total Weight 2.1.1 short-term 0.84 [0.59, 1.21] Becker,2010 76 1513 45 756 9.4% Huang,2014 0 344 1 172 0.3% 0.17 [0.01, 4.08] Jiang,2014 1.54 [0.07, 36.11] 1 40 0 20 0.1% Lu.2016 1 41 5 41 0.8% 0.20 [0.02, 1.64] Nong,2018 0 68 1 68 0.2% 0.33 [0.01, 8.04] Schumacher,2008 11 670 1 268 0.2% 4.40 [0.57, 33.91] Tang,2017 0.08 [0.01, 0.61] 44 12 44 1.9% 315 159 0.78 [0.40, 1.52] **0.74 [0.56, 0.99]** Wang,2013 20 13 2.7% Subtotal (95% CI) 3035 1528 15.6% 110 78 Total events Heterogeneity: $Chi^2 = 10.81$, df = 7 (P = 0.15); $I^2 = 35\%$ Test for overall effect: Z = 2.01 (P = 0.04) 2.1.2 long-term 1.46 [0.75, 2.84] Becker,2009 95 1288 178 2.5% 9 White,2018 82.0% 1.06 [0.96, 1.19] 1.08 [0.97, 1.20] 560 3098 525 3092 Subtotal (95% CI) 4386 3270 84.4% Total events 655 534 Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); $I^2 = 0\%$ Test for overall effect: Z = 1.35 (P = 0.18) Total (95% CI) 4798 100.0% 1.02 [0.93, 1.13] 765 Total events 612 Heterogeneity: Chi² = 15.47, df = 9 (P = 0.08); I^2 = 42% 0.01 0.1 10 100 Test for overall effect: Z = 0.47 (P = 0.64) Favours [experimental] Favours [control]

Supplementary Table 1: Methodological quality assessment of prospective cohort studies treating hyperuricemia and gout with uric-lowering therapies.

Test for subaroup differences: $\dot{C}hi^2 = 5.53$. df = 1 (P = 0.02). $I^2 = 81.9\%$

Authors	Year	Selection		ı	Comparability	me Asses	sment	Score		
		1	2	3	4	5	6	7	8	
Ekundayo	2010	*	*	*	*	**		*		7
Fang	2000	*	*	*	*	*	*	*		7
Franse	2000		*	*	*			*		4
Kanbay	2012		*	*	*		*			4
Sciacqua	2015		*	*	*	**	*	*		7
Turak	2014	*	*	*	*		*			5
Zalawadiya	2015	*	*	*	*		*	*		6