National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[l] Evidence reviews for diet and lifestyle modifications for managing gout

NICE guideline NG219

Evidence reviews underpinning recommendations 1.4.1 and 1.4.2 in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-4603-7

Contents

1 The clinical and cost effectiveness of diet and lifestyle modifications for gout

1.1 Review question: What is the clinical and cost effectiveness of diet and lifestyle modifications for gout?

1.1.1 Introduction

Gout has been associated with diet and lifestyle for centuries. How diet and lifestyle may influence gout is of interest to people living with gout, and people often self-initiate dietary change to help manage their gout. Current practice regarding diet and lifestyle modification for people living with gout varies widely. There is no standardised approach for diet and lifestyle modification advice in gout. Currently if people with gout are given advice regarding diet and lifestyle modification it may include advice to avoid excessive consumption of alcohol, high purine foods and sugar-sweetened soft drinks and also to support weight loss if overweight or obese. Advice may also be given to encourage a well-balanced diet with low fat dairy products, cherries, and adequate fluid intake. However, people with gout report that the advice received from health care professionals is often limited and information about diet can be conflicting and confusing.

Practice regarding the diet and lifestyle modification in gout varies greatly and there is also uncertainty regarding effectiveness of diet and lifestyle modification in the management of gout. This review was carried out to assess the clinical and cost effectiveness of diet and lifestyle modifications for gout.

The results were not stratified by whether the population had Chronic Kidney Disease (CKD) or not as the committee did not think the interventions would work differently in this group. However, CKD was added as a sub-group in order to investigate heterogeneity.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (18 years and older) with gout Strata: None Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout

Intervention(s)	Example of diet modifications and lifestyle modifications:
	• Lifestyle modifications (weight loss, smoking cessation, exercise)
	• Dietary modification:
	  ○ Elimination or reduced intake of; fructose-sweetened drinks, ethanol (particularly beer and spirits), purine-rich foods (particularly meat and seafood)
	  ○ reduced energy intake (e.g. weight reduction interventions) e.g. energy/calorie deficit, very low-calorie diet (VLCD)/very low energy diet (VLED), meal replacements, low carbohydrate diet, intermittent fasting.

	○ Increased intake of; coffee, dairy or vitamin C omega-3, Polyunsaturated Fatty Acids, rich fish, cherries, tomatoes, water. ○ Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines • Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C • Combination of diet and lifestyle modifications
Comparison(s)	• Urate-lowering medications (uricases, uricosuric agents, xanthine oxidase inhibitors); or • Other non-pharmacological interventions including lifestyle interventions or alternative diet (e.g. individualised diet based on gout management guidelines) used in treating gout. • Combination of interventions (e.g. diet and pharmacological) • Placebo (e.g. with some dietary supplement studies) • Usual care/information leaflet • Interventions compared to each other
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures (we would prioritise the health-related quality of life measures listed, but if they are not reported we would look at other validated gout-specific HRQoL measures). • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • adverse events and complications of gout: ○ radiographic joint damage ○ renal stones ○ tophi (total adverse events will be reported if the specific adverse events are not reported) • serum urate levels • admissions (hospital and A&E/urgent care) • GP visits Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration
Study design	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for lifestyle modifications and dietary modifications interventions/comparisons), a search for

	non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender Published NMAs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Seven randomised controlled trials included in this review[10, 14, 17, 31-33, 35]

One Cochrane review (Andres 2014)[2] and its analysis of two RCTs (Dalbeth 2012[10] and Stamp 2013[35]) was included in this review. Five RCTs (Holland 2015,[14] Juraschek 2021,[17] Schlesinger 2012,[31] Singh 2019,[32] and Stamp 2020[34] were added to this. One study[10] evaluated skimmed milk powder (SMP) enriched with glycomacropeptide (GMP) and milk fat extract (G600) versus control (SMP/lactose powder). One cross-over study[17] included DASH (the dietary approaches to stop hypertension) dietitian-directed groceries compared to self-directed groceries. Another study[14] looked at comprehensive dietary advice in addition to the advice on other interventions which the control group received. Cherry extract was evaluated in three studies.[31, 32, 34] These were analysed separately as they had different comparators (placebo, individualised diet modification and pomegranate juice). One study[35] evaluated vitamin C in comparison to allopurinol (in allopurinol naïve patients), and vitamin C compared to an increased dose of allopurinol, in patients who were already using allopurinol at baseline.

1.1.4.2 Excluded studies

RCTs were the preferred study design, however cohort studies were also included in the search. All cohort studies found looked at the risk of gout from diet, rather than the effect of dietary modifications on the person who has gout and were therefore excluded.

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Dalbeth 2012[10]	Intervention (n=40) Skim milk powder (SMP) enriched with glycomacropeptide (GMP) and milk fat extract (G600) (1.5 g GMP protein (10% total protein) and 0.525 g G600 (3.5% of total protein weight)) Intervention (n=80) Lactose powder/ Skim milk powder Lactose intervention was a cream-coloured powder administered daily as a 250 ml vanilla flavoured shake mixed in water by the patient using a wand blender. The lactose content of the lactose powder control was chosen to parallel the amount found in the SMP study products. Skim milk powder (SMP). The amount of SMP used in the SMP formulations was adjusted to give a total protein content of 15 g	n=120 All patients were aged ≥18 years old, had a diagnosis of gout (according to the American College of Rheumatology diagnostic classification) and were experiencing frequent gout flares at the time of study enrolment (at least two flares in the preceding 4 months). Age – mean years (SD): Lactose group: 56(17), SMP group: 56(12), SMP/GMP/G600 group: 56(13) Gender (M:F) – 108:12 Ethnicity: Caucasian: Lactose group -70%, SMP group - 70% SMP/GMP/G600 group - 55% Other ethnicities not reported New Zealand	HAQ-II – physical function at 3 months Pain during gout flares at 3 months Total adverse events (number of patients with at least 1 adverse event) at 3 months Serum uric acid, change score at 3 months	This study was included in the Cochrane review Andres 2014[2]

Study	Intervention and comparison	Population	Outcomes	Comments
Holland 2015[14]	Intervention (n=15) Comprehensive dietary advice. In addition to the advice given to control group, the intervention group received dietary advice in line with British Society for Rheumatology guidelines for the management of gout. The advice recommended the reduction of red meat intake, avoidance of offal, shellfish and yeast extract; and the inclusion of low fat dairy products, vegetables and cherries and the potential benefit of coffee and vitamin C. Comparison (n=14) The control group received advice regarding the importance of compliance with drug therapy, the benefit of weight loss and exercise (achieve ideal body weight) and the benefit of reduced alcohol intake. they were also advised on target urate concentration	n=29 Males and females aged >18 years with history of gout as per American College of Rheumatology criteria, who were on stable dose of urate lowering therapy at target (serum urate <0.36 mmol/L), were included in the study Age – mean years (range): Intervention group 64(44-80), Control group 61(38-77) Gender (M:F) – 27:2 Ethnicity: Not reported Australia	Flares at 6 months Serum urate level at 6 months	
Juraschek 2021[17]	Intervention 1 (n=22) Period 1: Dietitian directed groceries based on the DASH diet for four weeks. Period 2: self-directed grocery shopping (continue their typical dietary habits) for another four weeks	n=43 Eligible participants were community-dwelling adults, aged 18 years, with a self-reported diagnosis of gout and a SU concentration ≥7 mg/dL. Patients were not taking urate lowering therapy	Serum urate level at 1	This was a crossover study with no washout period. Only the data from period 1 was used. Adverse events were reported as an odds ratio and could not be used in this review.

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison 2 (n=21) Period 1: Self-directed grocery shopping for four weeks (as above) Period 2: then patients crossed over to dietitian directed (DASH) groceries for four weeks (as above)	Age – mean years (SD): 59(12.1) Gender (M:F) -35:8 Ethnicity (%): Black – 49% Other ethnicities - not reported USA		
Schlesinger 2012[31]	Intervention (n=9) Cherry juice concentrate tablespoon twice daily for four months Comparison (n=5) Pomegranate concentrate juice tablespoon twice daily for four months	n=14 Eighteen patients with MSU crystal- proven gout were entered into this study Age – mean years (SE): 56.43 (4.1) Gender (M:F) – not reported Ethnicity: Caucasian - 11 (78.57%), Asian - 1 (7.14%), Hispanic - 1 (7.14%), African American 1 (7.14%), USA	Flares (number of flares and number of people with at least 1 gout flare) at 4 months Serum urate level at 4 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Singh 2019 [32] (Singh 2020)[33]	Intervention (n=41) Cherry extract 3,600 mg daily (3 capsules of 1200 mg each daily, each equivalent to 32 oz of cherry juice or a pound of cherries. Patients were sent the 3-month supply of cherry capsules, to each study participant at 3, 6, and 9 months, supplemented with study coordinator calls to encourage cherry extract adherence. Comparison (n=43) Diet modification. Patients were sent individualized diet recommendation (based on baseline FFQ data) to each study participant at 3, 6, and 9 months, supplemented with dietitian calls to discuss specific recommendations.	n=84 US adults aged 18 years or older with a valid US mailing address and e-mail address and patient self-reported physician diagnosis of gout. Age – mean years (SD): Cherry extract group: 58.2(15.5), Diet modification group: 53.6(11.9) Gender (M:F) – 61:23 Ethnicity: Cherry extract group - White 30(73%), Black or African American - 9(22%), Asian/other/mixed - 2 (5%). Diet modification group. White 27(63%), Black or African American 12(28%), Asian/other/mixed 4 (9%). USA	Frequency of gout flares (proportion with any gout flare) HAQ-DI at 9 months Any adverse event (not including gastrointestinal adverse events) at 9 months Specific gastrointestinal adverse events at 9 months Average pain score at 9 months Serum urate level at 9 months Number achieving sUA <6mg/dL at 9 months Number achieving sUA <5mg/dL at 9 months	
Stamp 2013[35]	Patients not taking allopurinol at baseline: Intervention (n=10) Supplemental vitamin C 500 mg per day	n=40 Patients with gout, whose diagnosis was defined according to the American College of Rheumatology preliminary	Serum urate level, change score at 2 months	This study was included in the Cochrane review Andres 2014[2] Randomisation of patients was stratified according to allopurinol use at baseline

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=10) Allopurinol up to 100mg per day. Allopurinol was started at 50mg or 100mg. Patients already taking allopurinol at baseline: Intervention (n=10) Supplemental vitamin C at a dosage of 500 mg/day Comparison (n=10) Allopurinol increased dose. Allopurinol was increased by 50 mg or 100mg increments, at the discretion of the physician, depending on each patient's renal function and comorbidities. The dose of allopurinol was further increased at 4 weeks if the patient had not achieved the target SU level of <0.36 mmols/liter (6 mg/dl)	criteria (10), and with an SU level >0.36 mmols/L (6 mg/dl) were recruited comprising 20 who were already receiving allopurinol and 20 who had not received any urate lowering therapy. Age – mean years (range): Vitamin C group 61.2 (39-86) Allopurinol group 55 (27-78) Gender (M:F) – 36:4 Ethnicity: New Zealand - European 25(62.5%) Other – 15 (37.5%) New Zealand		
Stamp, 2020[34]	Intervention (n=40) 7.5/ 15/ 22.5/ 30 ml of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with Cherry Concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about	n=50 Patients with gout, whose diagnosis was defined according to the American College of Rheumatology preliminary criteria and with an SU level >0.36 mmols/L (6 mg/dl) were recruited	Serum urate level at 28 days Number of gout flares Number of patients with adverse events Number of hospital admissions	The 4 intervention groups (different doses of cherry juice concentrate) were combined for the analyses. 50% of patients in each of the 5 randomised groups were taking allopurinol.

Study	Intervention and comparison	Population	Outcomes	Comments
	15g sugar per 30 mls). Duration 28 days. Comparison (n=10. Placebo (2 drops of cherry juice concentrate in water).	comprising 25 who were already receiving allopurinol and 20 who had not received any urate lowering therapy. Age Mean (SD): Placebo group: 56.9 (12.9) 7.5ml group: 63.3 (13.0), 15ml group: 61.0 (9), 22.5ml group: 56.2 (11.4), 30ml group: 60.4 (11.6). Gender (M:F) – Placebo group: 9M/1F 7.5ml group: 9M/1F, 15ml group: 9M/1F, 22.5ml group: 8M/2F, 30ml group: 10M/0F. Ethnicity: Placebo group: NZ European 4, Maori/ Pacific 6 7.5ml group: NZ European 9, Maori/ Pacific 1 15ml group: NZ European 7, Maori/ Pacific 3 22.5ml group: NZ European 7, Maori/ Pacific 3 30ml group: NZ European 8, Maori/ Pacific 2 New Zealand		

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: enriched skimmed milk powder (SMP) GMP/G600) versus control (SMP/lactose) – Cochrane review data

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (SMP/lactose)	Risk difference with SMP (GMP/G600) versus SMP/lactose (95% CI)
Physical function HAQ-II (0-3)	104 (1 study) 3 months	HIGH	-	mean 0.11	MD 0.03 lower (0.14 lower to 0.08 higher)
Pain during gout flares – change score (0-10 Likert Scale)	104 (1 RCT) 3 months	MODERATE[a]	-	mean 0.94	MD 1.03 lower (1.89 lower to 0.17 lower)
Number of gout flares per month, after 3 months	120 (1 RCT) 3 months	MODERATE[a]	-	mean 0.6997	MD 0.21 lower (0.76 lower to 0.34 higher)
Total adverse events (number of patients with at least 1 adverse event)	120 (1 RCT) 3 months	LOW[a]	-	350 per 1,000	18 fewer per 1,000 (136 fewer to 172 more)
Serum uric acid reduction (change score)	120 (1 RCT) 3 months	MODERATE[a]	-	mean 0.0101 mmo/L	MD 0.01 lower (0.04 lower to 0.01 higher)

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for HAQ-II – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The MID for pain during gout flares was calculated as 0.825;

Table 4: Clinical evidence summary: dietitian directed groceries versus self-directed groceries

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (self-directed groceries)	Risk difference with dietician-directed DASH groceries (95% CI)
Serum urate level, change score	43 (1 RCT) 1 month	LOW[a,b]	-	mean was 0 mg/dL	MD 0.55 lower (1.2 lower to 0.1 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The MID calculated for serum urate level was 0.38.

Table 5: Clinical evidence summary: cherry extract versus individualised diet modification

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (individualised diet)	Risk difference with cherry extract versus individualised diet modification (95% CI)
HAQ-DI (scale 0-3) at 9 months	84 (1 RCT)	VERY LOW[a,b]	-	mean 0.23	MD 0.05 higher (0.15 lower to 0.25 higher)
Average pain score (0-10) in the last 24 hours	58 (1 RCT)	VERY LOW[a,b]	-	mean 0.85	MD 0.01 lower (0.83 lower to 0.81 higher)
Proportion with any gout flare at 9 months	84 (1 RCT)	VERY LOW[a,b]	RR 0.86 (0.61 to 1.22)	651 per 1,000	91 fewer per 1,000 (254 fewer to 143 more)
Any adverse event at 9 months	58 (1 RCT)	VERY LOW[a,b]	Peto OR 6.13 (0.12 to 315.32)	0 per 1,000	30 more per 1,000 (60 fewer to 120 fewer)
Specific gastrointestinal adverse events at 9 months	58 (1 RCT)	VERY LOW[a,b]	RR 1.04 (0.45 to 2.42)	269 per 1,000	11 more per 1,000 (148 fewer to 382 more)
Serum urate level at 9 months	84 (1 RCT)	MODERATE[a]	-	mean 7mg/dL	MD 0.16 higher (0.61 lower to 0.93 higher)
Number of patients achieving sUA <6mg/dL at 9 months	65 (1 RCT)	VERY LOW[a,b]	RR 0.80 (0.33 to 1.94)	258 per 1,000	52 fewer per 1,000 (173 fewer to 243 more)
Number of patients achieving sUA <5mg/dL at 9 months	65 (1 RCT)	VERY LOW[a,b]	RR 0.36 (0.08 to 1.75)	161 per 1,000	103 fewer per 1,000 (148 fewer to 121 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (individualised diet)	Risk difference with cherry extract versus individualised diet modification (95% CI)
for HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for pain was 1.5; and for serum urate level was 0.99.					

Table 6: Clinical evidence summary: cherry extract versus placebo (in a mixed population taking and not taking allopurinol at baseline)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (placebo)	Risk difference with cherry extract versus placebo (95% CI)
Serum urate follow up: 28 days	50 (1 RCT)	LOW[a]	-	The mean serum urate was 0.47	MD 0.04 lower (0.12 lower to 0.04 higher)
Number of gout flares follow up: 28 days	50 (1 RCT)	VERY LOW[a,b]	-	The mean number of gout flares was 0.4	MD 0.1 higher (0.25 lower to 0.45 higher)
Adverse events follow up: 28 days	50 (1 RCT)	VERY LOW[a,b]	RR 0.75 (0.41 to 1.38)	600 per 1,000	150 fewer per 1,000 (354 fewer to 228 more)
Hospital admissions assessed with: serious adverse events follow up: 28 days	50 (1 RCT)	VERY LOW[a,b]	Peto OR 3.58 (0.11 to 118.71)	0 per 1,000	50 fewer (90 fewer to 190 more)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE defaults MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for serum urate level was 0.4; and for gout flares was 0.25.					

Table 7: Clinical evidence summary: cherry juice concentrate versus pomegranate juice concentrate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (pomegranate juice)	Risk difference with cherry juice concentrate versus pomegranate juice (95% CI)
Flares (number of people with at least 1 flare) at 4 months	14 (1 RCT)	VERY LOW[a,b]	RR 0.56 (0.24 to 1.30)	800 per 1,000	352 fewer per 1,000 (608 fewer to 240 more)
Serum urate level (mg/dL) at 4 months	14 (1 RCT)	LOW[a,b]	-	mean 6.14 mg/dL	MD 2.03 higher (0.98 lower to 5.04 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used;for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for serum urate level is 0.96.

Table 8: Clinical evidence summary: comprehensive dietary advice versus basic dietary advice

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (basic dietary advice)	Risk difference with comprehensive versus basic dietary advice (95% CI)
Flares at 6 months	29 (1 RCT)	VERY LOW[a,b]	RR 0.54 (0.05 to 5.28)	133 per 1,000	61 fewer per 1,000 (127 fewer to 571 more)
Serum urate level at 6 months	29 (1 RCT)	LOW[a,b]	-	mean 0.27 mmol/L	MD 0.03 higher (0.02 lower to 0.08 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (basic dietary advice)	Risk difference with comprehensive versus basic dietary advice (95% CI)
MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The MID for serum urate level was calculated at 0.35.					

Table 8: Clinical evidence summary: vitamin C versus allopurinol (in people not taking allopurinol at baseline) – Cochrane review data

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (allopurinol)	Risk difference with vitamin C versus allopurinol (95% CI)
Serum urate level (change score) at 2 months	20 (1 RCT)	LOW[a]	-	mean -0.15 mmol/L	MD 0.15 higher (0.08 higher to 0.22 higher)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. GRADE default MIDS were used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for serum urate level was 0.44.					

Table 9: Clinical evidence summary: allopurinol and vitamin C versus increased dose of allopurinol (in people taking allopurinol at baseline) – Cochrane review data

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (allopurinol)	Risk difference with vitamin C versus allopurinol (95% CI)
Serum urate level at 8 weeks (change score)	20 (1 RCT)	VERY LOW [a,b]	-	mean -0.09 mmol/L	MD 0.06 higher (0.01 lower to 0.13 higher)
a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (allopurinol)	Risk difference with vitamin C versus allopurinol (95% CI)
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for serum urate level was 0.44.					

See Appendix F for full GRADE

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but excluded due to limited applicability[5]. This study is listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 10: Staff costs

Resource	Unit costs
Primary care Practice Nurse (Band 5), cost per hour[(a)]	£42
General Practitioner, cost per consultation (9.22 minutes)[(a)]	£37
Dietitian Band 5 / Band 6, cost per hour[(a)]	£39 / £51

Source: PSSRU, 2020[3]
(a) Including qualification costs but excluding individual and productivity costs.

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered the following outcomes as important for decision-making: health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, frequency of flares, patient global assessment of treatment success, adverse events (total), adverse events and complications of gout (radiographic joint damage, renal stones, tophi), serum urate levels, admission (hospital and A&E/urgent care) and GP visits.

The committee decided to combine joint swelling and joint inflammation as they agreed that these outcomes are synonymous for people with gout. The committee also agreed to categorise timepoints reported in the included studies by short-term (up to three months), medium-term (three to twelve months) and long-term (more than twelve months).

1.1.11.2 The quality of the evidence

Seven randomised control trials were included in the evidence review and one Cochrane review[2] reported on two of the trials. The studies looked at different dietary interventions or the comparisons varied so they were unable to be meta-analysed. All studies included were diet modifications, none focused on lifestyle modifications.

One study, included in the Cochrane review, evaluated enriched skim milk powder (SMP) (GMP/G600) compared to SMP/lactose for physical function (HAQ-II), pain, number of gout flares per month and total number of adverse events at medium-term (three months). The quality of evidence ranged from low to high due to imprecision.

One study evaluated cherry extract versus individualised diet modification. The outcome data was reported for a number of outcomes: disability (HAQ-DI), average pain score, proportion of patients with any gout flare, any adverse event, specific gastrointestinal adverse events, serum urate level and number of patients achieving sUA <6mg/dL and sUA <5mg/dL. All outcomes were reported at short to medium-term (28 days to 9 months). The quality of evidence was very low for all outcomes, due to risk of bias (lack of blinding) and imprecision, except for serum urate level which was moderate (due to the objective nature of the outcome). Evidence from one study investigated cherry juice compared to placebo in a mixed allopurinol population, measured in the short term (28 days). The outcomes (serum urate level, number of gout flares, adverse events and hospital admissions) were graded from low to very low, due to risk of bias (possible selection bias and lack of blinding). This study also had four cherry groups which were combined (n=40) and so the placebo arm only had 10 participants. Another study investigated a cherry juice concentrate versus pomegranate juice concentrate. The outcome data was reported for flares (number of people with at least 1 gout flare) and serum urate level, both outcomes reported at medium-term (four months). The quality of evidence ranged from low to very low due to risk of bias (no blinding and unclear comparability of care) and imprecision. The committee were not aware of pomegranate juice as a recognised dietary change for gout, so may be considered indirect for this review but it did meet the protocol as a dietary modification and so was not downgraded. Furthermore, this was a pilot study and only included 14 participants, with only 5 in the pomegranate arm. All the studies were small and most had risk of bias therefore, the committee had a lack of confidence in any benefits shown for cherry juice.

One study, included in the Cochrane review, evaluated vitamin C versus allopurinol, in people taking or not taking allopurinol at baseline. The analysis was presented separately. The non-allopurinol at baseline group received allopurinol versus vitamin C. Only one outcome, serum urate level, was assessed and the quality of this outcome was low due to risk of bias. The other arm evaluated allopurinol and vitamin C versus an increased dose of allopurinol (in people taking allopurinol at baseline) and was graded very low due to risk of bias (possible selection bias, lack of blinding and unclear comparability of care) and imprecision.

Another study evaluated dietitian-directed groceries compared to self-directed groceries. The outcome data was reported for only one outcome, serum uric acid change (from baseline) at short-term (up to three months). The quality of evidence was low due to risk of bias (lack of blinding) and imprecision. The study was a cross-over study but as there was no washout period the second period of the crossover study was not included due to possible carry-over effect.

One study evaluated comprehensive dietary advice versus basic dietary advice. The outcome data was reported for frequency of flares and serum urate level, both outcomes were reported at medium-term (6 months). The quality ranged from low to very low due to risk of bias (incomplete outcome data) and imprecision.

The committee agreed that overall, the evidence was limited, as there was only one study per comparison and the quality of outcomes was mostly low to very low due to risk of bias

and imprecision. The studies were very small, with uncertainty in the effect sizes and most were conducted in the short term, therefore the committee could not be confident in the evidence to use as a basis for recommendations. The committee acknowledged the difficulty in conducting studies on dietary modification, such as monitoring participants' compliance with the diet and dietary intake during studies and obtaining accurate results over a long enough time period. The committee discussed whether to make a research recommendation but concluded this was not a priority area and agreed individual dietary factors (except alcohol) are unlikely to have any significant impact on reducing flares or lowering serum urate levels.

1.1.11.3 Benefits and harms

The evidence showed no clinical difference for physical function (HAQ-II), pain, number of gout flares per month, total number of adverse events and serum urate reduction when comparing enriched skimmed milk powder (SMP) (GMP/G600) to SMP/lactose at medium-term (at three months).

There was a clinical benefit for cherry extract when compared to individualised diet modification for a proportion of patients with any gout flare outcome at medium-term (9 months), however there was uncertainty around the effect size. For the number of patients achieving a target serum urate level <6mg/dL and <5mg/dL, the evidence showed clinical benefit for individualised diet at medium-term (9 months). There was no clinical difference for disability (HAQ-DI), average pain score, adverse events (any), gastrointestinal adverse events and serum urate level at medium-term (9 months). Evidence from one study showed no clinical benefits of cherry extract compared to placebo at 28 days for serum urate level or gout flares. There was a clinical benefit of reduction in adverse events and hospital admissions, but there was uncertainty around the effect sizes. Quality of the outcomes were graded low to very low. A clinical benefit was found for cherry juice concentrate when compared to pomegranate juice for frequency of flares (number of people with at least 1 flare) at medium-term (4 months), but there was uncertainty around the effect size. There was no clinical difference in serum urate level at medium-term (4 months). As the committee were not aware of pomegranate juice as a dietary modification for gout, they were uncertain whether this could be considered an active comparator.

The evidence showed no clinical difference for vitamin C versus allopurinol (in people not taking allopurinol at baseline) nor allopurinol and vitamin C versus increased dose of allopurinol (in people taking allopurinol at baseline) for serum urate level (change score) at short-term (up to three months).

There was no clinical difference for serum urate level change score when comparing dietitian-directed groceries compared to self-directed groceries at short-term (up to three months).

The evidence did show clinical benefit for comprehensive dietary advice when compared to basic dietary advice for frequency of flares outcome at medium-term (three to twelve months), but there was uncertainty around the effect size. There was no clinical difference for serum urate level outcome at medium-term (three to twelve months).

The committee agreed there was not strong enough evidence to support any specific diet. There were clinical benefits of cherry juice extract compared to individualised diet modification for a proportion of people with any gout flares but there was also clinical benefit for the diet modification arm for serum urate levels <5mg/dL and <6mg/dL at 9 months. Cherry extract compared to placebo showed fewer adverse events and hospital admissions but no difference for flares or serum urate levels. Cherry juice consumption also resulted in fewer flares than with pomegranate juice, and comprehensive dietary advice was found to have a clinical benefit for flares at 6 months compared to basic dietary advice. However, the studies were small, single studies of low to very low quality with short follow-up, therefore the committee concluded the evidence was not robust enough to support any specific diet, and

also acknowledged the dietary interventions considered in the studies would be hard to translate into practice. They also discussed that a significant proportion of people with gout have other comorbidities and may already have received advice on dietary requirements for other conditions and were therefore conscious of possibly providing conflicting advice. The committee recognised many people with gout are aware of a connection between the condition and diet, and advice about diet is frequently asked for by patients. The consensus of the committee was that lifestyle modification, such as maintaining a healthy weight and encouraging a healthy diet would have a greater impact on improving a person's gout along with taking urate lowering therapy prescribed. The committee therefore agreed to recommend following a healthy balanced diet. There was consensus that weight and alcohol consumption should be mentioned within the recommendation as there is epidemiological evidence that increased weight and high alcohol consumption is associated with gout. [8, 9, 12]

1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question. Unit costs were presented to aid to committee consideration of cost effectiveness.

The committee discussed the evidence presented noting there was limited clinical evidence which was generally of low quality and poor study design. Therefore, the committee concluded they could not make a specific recommendation with regards to diet and lifestyle modifications for people with gout. The committee did however note that all people with gout should be advised to lead a healthy lifestyle because excess body weight, obesity, or excessive alcohol consumption may exacerbate gout flares and symptoms of gout. The committee made reference to NICE's guidance on preventing excess weight gain (2015) and obesity: identification, assessment and management (2014).

The committee noted that in current practice discussions regarding diet and lifestyle with health care professionals (such as a GP) already occur because these conversations are typical initiated by patients due to their awareness of a historical link between diet and gout. Overall, the recommendations made are in line with current practice and therefore not expected to result in a substantial resource impact.

1.1.11.5 Other factors the committee took into account

The committee acknowledged the BSR guideline recommendations on diet advising reducing weight in patients who are overweight, promoting a diet low in fat and sugars and high in fibre, and avoiding excessive alcohol intake. The committee agreed existing NICE guidance on preventing excess weight gain provided generic recommendations and reflected similar advice clinicians would give to people with gout. The committee also agreed cross reference should be made to the Obesity: identification, assessment and management guideline.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.2.

1.1.13 References

Appendices

Appendix A – Review protocols

Review protocol for the clinical and cost-effectiveness of diet and lifestyle modifications for gout

ID	Field	Content
0.	PROSPERO registration number	CRD42021246152
1.	Review title	The clinical and cost effectiveness of diet and lifestyle modifications for gout
2.	Review question	What is the clinical and cost effectiveness of diet and lifestyle modifications for gout?
3.	Objective	To determine which diet and lifestyle modifications are the most clinically and cost-effective for gout
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details) Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Gout (including people with gout and chronic kidney disease)

6.	Population	Inclusion: Adults (18 years and older) with gout Strata: None Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.
7.	Intervention/Exposure/Test	Example of diet modifications and lifestyle modifications: • Lifestyle modifications (weight loss, smoking cessation, exercise • Dietary modification: - Elimination or reduced intake of; fructose-sweetened drinks, ethanol (particularly beer and spirits), purine-rich foods (particularly meat and seafood) - reduced energy intake (i.e. weight reduction interventions) e.g. energy/calorie deficit, very low calorie diet (VLCD)/very low energy diet (VLED), meal replacements, low carbohydrate diet, intermittent fasting. - Increased intake of; coffee, dairy or vitamin C omega-3, Polyunsaturated Fatty Acids, rich fish, cherries, tomatoes, water. - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines • Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C • Combination of diet and lifestyle modifications
8.	Comparator/Reference standard/Confounding factors	• Urate-lowering medications (uricases, uricosuric agents, xanthine oxidase inhibitors); or • Other non-pharmacological interventions including lifestyle interventions or alternative diet (e.g individualised diet based on gout management guidelines) used in treating gout. • Combination of interventions (e.g. diet and pharmacological) • Placebo (e.g. with some dietary supplement studies) • Usual care/information leaflet • Interventions compared to each other

9.	Types of study to be included	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for lifestyle modifications and dietary modifications), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender Published NMAs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	There are a variety of diet and lifestyle modifications which are available to people with gout, this review looks at what the benefits are from such modifications.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures (we would prioritise the health-related quality of life measures listed, but if they are not reported we would look at other validated gout-specific HRQoL measures). • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • adverse events and complications of gout:

		○ radiographic joint damage ○ renal stones ○ tophi (total adverse events will be reported if the specific adverse events are not reported) • serum urate levels • admissions (hospital and A&E/urgent care) • GP visits Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Evibase will be used for data extraction. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

		• Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. If sufficient data is available and it is methodologically appropriate, network meta-analysis (NMA) will conducted. NMA will be prioritised for the following outcomes, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence: • Serum urate levels • Frequency of flares • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

<table>
<tr><td></td><td></td><td colspan="3">• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
• WinBUGS will be used for network meta-analysis, if possible given the data identified.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups that will be investigated if heterogeneity is present:
• Setting (primary and secondary)
• BMI (BMI 18.5 to 24.9 (healthy weight); BMI 25 or over (overweight); or BMI 30 or over (obese).CKD stage (People with CKD (stage 3), people with CKD (stages 4-5), people without CKD or people with CKD stages 1-2, mixed population (people with CKD and people without CKD)</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">14th January 2020</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">13th June 2022</td></tr>
<tr><td rowspan="4">23.</td><td rowspan="4">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
</table>

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Julie Neilson [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the		

		manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]	
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	[Give words or phrases that best describe the review.]	
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[25] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- What is the clinical and cost effectiveness of diet and lifestyle modifications for gout?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[25]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 7 of 12 CENTRAL to 2021 Issue 7 of 12	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/

11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	Limit 25 to English language
27.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Epidemiologic studies/
47.	Observational study/
48.	exp Cohort studies/
49.	(cohort adj (study or studies or analys* or data)).ti,ab.
50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	Controlled Before-After Studies/
53.	Historically Controlled Study/
54.	Interrupted Time Series Analysis/
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control studies/
57.	case control*.ti,ab.
58.	Cross-sectional studies/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/46-59
61.	26 and (34 or 45 or 60)

Embase (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.
28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
30.	crossover procedure/
31.	single blind procedure/

32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Clinical study/
47.	Observational study/
48.	family study/
49.	longitudinal study/
50.	retrospective study/
51.	prospective study/
52.	cohort analysis/
53.	follow-up/
54.	cohort*.ti,ab.
55.	53 and 54
56.	(cohort adj (study or studies or analys* or data)).ti,ab.
57.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
58.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	exp case control study/
61.	case control*.ti,ab.
62.	cross-sectional study/
63.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
64.	or/46-52,55-63
65.	24 and (34 or 45 or 64)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Gout] explode all trees
#2.	gout*:ti,ab
#3.	toph*:ti,ab
#4.	podagra:ti,ab
#5.	pseudogout:ti,ab

#6.	(or #1-#5)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1946 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1974 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	Uric Acid/
5.	uric acids*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter/
12.	editorial/
13.	news/

14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.
53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.

55.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
56.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
57.	(hui or hui1 or hui2 or hui3).ti,ab.
58.	(health* year* equivalent* or hye or hyes).ti,ab.
59.	discrete choice*.ti,ab.
60.	rosser.ti,ab.
61.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
62.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
63.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
64.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
65.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
66.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
67.	or/48-66
68.	30 and (47 or 67)

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/
5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26

28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/
46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	28 and (42 or 64)

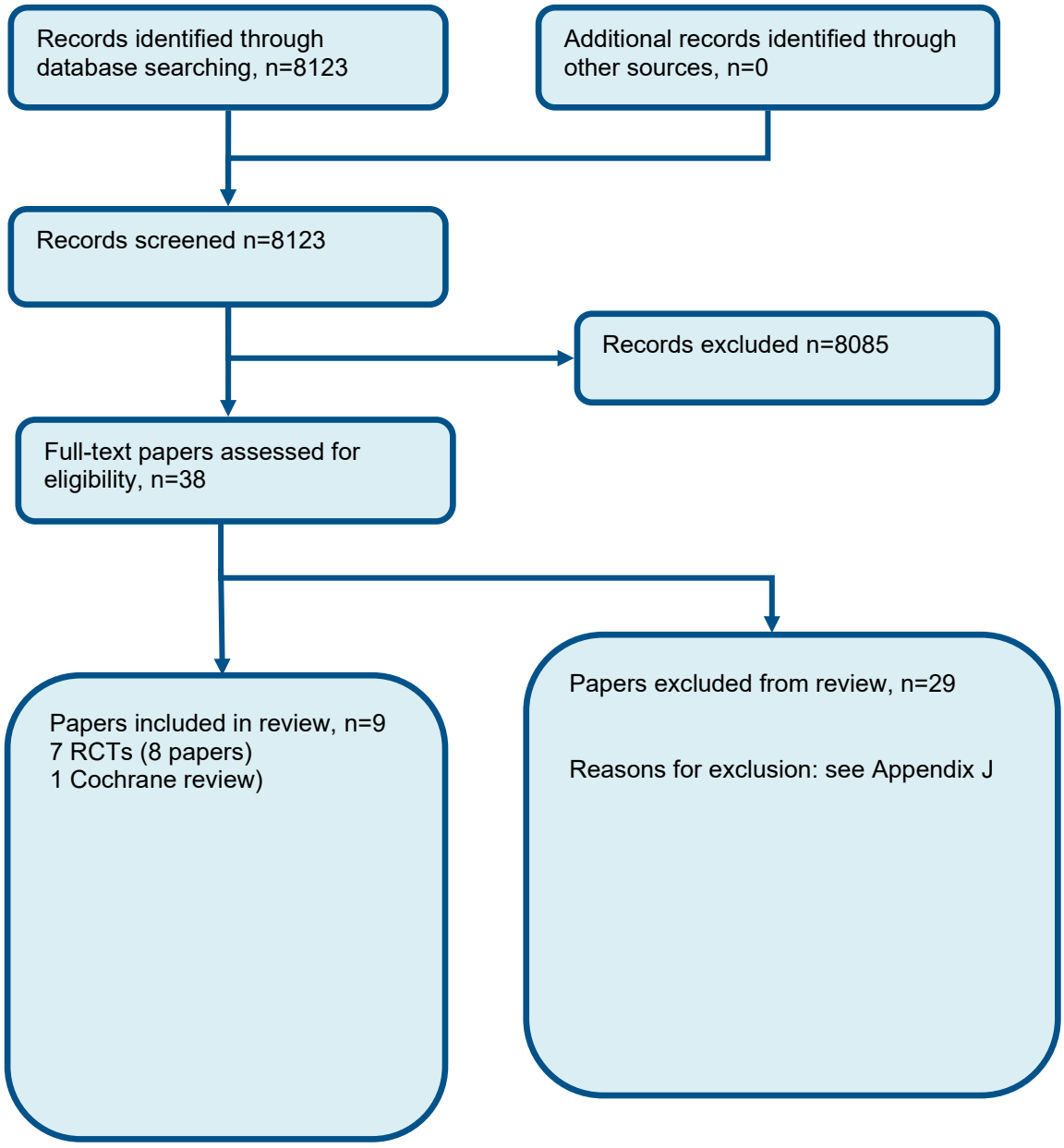
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES
#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES

#5.	(uric acid*)
#6.	((urate near (crystal* or sodium or mono sodium)))
#7.	MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES
#8.	((hyperuric* or hyper uric*))
#9.	(podagra)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of diet and lifestyle modifications for gout



Appendix D – Effectiveness evidence

Study	Dietary supplements for chronic gout (Cochrane review) trial: Andrés 2014[2]
Study type	Systematic Review
Number of studies (number of participants)	2 (n=160)
Countries and setting	Conducted in New Zealand; Setting: Rheumatology clinic/ Unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: average 10 weeks (3months and 8 weeks)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American College of Rheumatology diagnostic classification/ preliminary criteria
Stratum	Overall
Subgroup analysis within study	Not applicable: subgroup analysis was reported for whether or not patients were allopurinol naive.
Inclusion criteria	Cochrane review protocol: Types of studies: RCTs, quasi-RCTs (clinical controlled trials, CCTS) that compare dietary supplements with no supplements, placebo, another supplement or pharmacological agents for chronic gout were considered for inclusion. Only trials that were publishes as full articles or available as a full trial report were included. Types of participants: adults ages 18 years or older with a diagnosis of chronic gout. Interventions: trials were included evaluating any dietary supplement including, but not limited to, amino acids, antioxidants, PUFAs, prebiotics, vitamins, alone or in combination. All doses and administration routes were examined. Comparators could have been: placebo, no treatment, a different dietary supplement, pharmacological therapy, non-pharmacological therapy or combination therapy.

Exclusion criteria	Trials in acute gout where the aims of treatment were different, namely to reduce acute inflammation, studies that incorporated a mix of people with gout and other musculoskeletal diseases unless the results of the people with gout could be separated out for analysis.
Recruitment/selection of patients	Dalbeth: Patients were recruited from rheumatology clinics and by public advertisement. Stamp: not reported
Age, gender and ethnicity	Age - Other: Dalbeth mean (SD): 57 (16), Stamp: mean (range): 61.2 (39-86). Gender (M:F): Dalbeth: (M:F): 108/12; Stamp: (M:F): 36/4. Ethnicity: Dalbeth: Caucasian: Lactose group 70%, SMP 70% ,SMP/GMP/G600 55% Overall: 58% Caucasian Stamp: New Zealand European 15 (37.5%), Other 25(62.5%)
Further population details	1. BMI: Systematic review: mixed (Dalbeth:BMI: Not stated / Unclear, Stamp: BMI: BMI 30 or over (obese)). 2. CKD stage : Mixed population (people with CKD and people without CKD) (Dalbeth: CKD stage: Not stated / Unclear; Stamp: CKD stage : People with CKD (stages 1-2)).
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. SMP/ lactose. Duration 3 months. Concurrent medication/care: none reported. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed Comments: SMP and lactose group combined for analysis. (n=40) Intervention 2: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. SMP enriched with GMP and G600 (GMP protein 1.5g (10% total protein) and G600 0.525g (3.5% of total protein weight). Duration 3 months. Concurrent medication/care: none reported. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed (n=10) Intervention 3: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. vitamin C 500mg daily. Duration 8 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed Comments: People not taking allopurinol at baseline

	(n=10) Intervention 4: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Allopurinol 50-100mg daily (dose adjustment at 4 weeks based on sUA level). Duration 8 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed Comments: People not taking allopurinol at entry (n=10) Intervention 5: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Vitamin C 500mg daily(added to stable dose of allopurinol). Duration 8 weeks. Concurrent medication/care: Stable dose of allopurinol. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed Comments: People taking allopurinol at baseline (n=10) Intervention 6: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Allopurinol 50-100mg daily (increased the allopurinol dose, no specified dose scheme). Duration 8 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness Further details: 1. Setting: Systematic review: mixed Comments: People taking allopurinol at baseline
Funding	Other (Dalbeth 2012 was funded by LactoPharma (a joint venture between Fonterra Ld, Fonterra R&D Ltd and Auckland UniServices Ltd) and the New Zealand government Foundation for Research science and Technology. Barbara Kuhn-Sherlock, Alastair MAcGibbonand Kate Palamo are employees of Fonterra Co-operative group Ltd. AlastairMacGibbon, Nicola Dalbeth and KAte Palamo are named inventors on a patent application related to milk products and gout, although it says that 'data analysis was completed by a biostatistician independent of the study sponsors'. Stamp was independent research carried out with no relation to vitamin C or allopurinol producers.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SMP/ GMP/ G600 versus SMP/ LACTOSE (CONTROL) Protocol outcome 1: Quality of life medium-term (3 to 12 months) - Actual outcome: HAQ-II Physical function at 3 months; Group 1: mean 0.08 (SD 0.23); n=35, Group 2: mean 0.11 (SD 0.319); n=69; Health assessment questionnaire (HAQ-II) 0-3 Top=High is poor outcome	

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 2: Pain short-term medium-term (3 to 12 months)
- Actual outcome: Pain during gout flares at 3 months; Group 1: mean -1.97 (SD 2.28); n=40, Group 2: mean -0.94 (SD 2.25); n=-80; Likert scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Frequency of flares medium-term (3 to 12 months)
- Actual outcome: Number of gout flares per month at After 3 months; Group 1: mean 0.4928 (SD 1.52); n=40, Group 2: mean 0.7 (SD 1.28); n=80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Proportion of participants who reach serum urate target level medium-term (3 to 12 months)
- Actual outcome: Serum urate reduction at 3 months; Group 1: mean 0.0248 (SD 0.0668); n=33, Group 2: mean -0.01 (SD 0.0686); n=69
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 7; Group 2 Number missing: 11

Protocol outcome 5: Total adverse events (3 to 12 months)
- Actual outcome: Withdrawal due to adverse events at 3 months; Group 1: 7/40, Group 2: 11/80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VITAMIN C 500MG DAILY (PEOPLE NOT ALREADY TAKING ALLOPURINOL) versus ALLOPURINOL 50-100MG DAILY (PEOPLE NOT ALREADY TAKING ALLOPURINOL)

Protocol outcome 1: Proportion of participants who reach serum urate target level medium-term (3 to 12 months)
- Actual outcome: Serum urate reduction at 8 weeks; Group 1: mean -0.004 (SD 0.0791); n=10, Group 2: mean -0.15 (SD 0.0791); n=10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported in risk of bias; Blinding details: Dalbeth study was blinded, Stamp was open-

label.; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VITAMIN C 500MG DAILY (PEOPLE ALREADY TAKING ALLOPURINOL) versus ALLOPURINOL 50-100MG DAILY (PEOPLE ALREADY TAKING ALLOPURINOL)

Protocol outcome 1: Proportion of participants who reach serum urate target level short-term (less than 3 months)
- Actual outcome: Serum urate reduction at 8 weeks; Group 1: mean -0.03 (SD 0.0759); n=10, Group 2: mean -0.09 (SD 0.0791); n=10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: Dalbeth study was blinded, Stamp was open-label.; Group 1 Number missing: 0; Group 2 Number missing: 0

ROBIS quality assessment of systematic reviews

Study eligibility criteria: low concerns

Identification and selection of studies: low concerns

Data collection and study appraisal: low concerns

Synthesis and findings: low concerns

Risk of bias in the review: low concerns

Protocol outcomes not reported by the study	Quality of life short-term (less than three months) at Define; Quality of life Long-term (more than 12 months) at Define; Pain short-term (less than 3 months) at Define; Pain short-term Long-term (more than 12 months) at Define; Joint swelling/inflammation short-term (less than 3 months) at Define; Joint swelling/inflammation medium-term (3 to 12 months) at Define; Joint swelling/inflammation long-term (more than 12 months) at Define; Joint tenderness short-term (less than 3 months) at Define; Joint tenderness medium-term (3 to 12 months) at Define; Joint tenderness long-term (more than 12 months) at Define; Frequency of flares short-term (less than 3 months) at Define; Frequency of flares long-term (more than 12 months) at Define; Patient global assessment of treatment success short-term (less than three months) at Define; Patient global assessment of treatment success medium-term (3 to 12 months) at Define; Patient global assessment of treatment success long-term (more than 12 months) at Define; Proportion of participants who reach serum urate target level long-term (more than 12 months) at Define; Radiographic joint damage (less than 3 months) at Define; Radiographic joint damage (3 to 12 months) at Define; Radiographic joint damage (more than 12 months) at Define; Renal stones (less than 3 months) at Define; Renal stones (3 to 12 months) at Define; Renal stones (more than 12 months) at Define; Tophi short-term (less than 3 months) at Define; Total adverse events (less than 3 months) at Define; Tophi

	medium-term (3 to 12 months) at Define; Tophi long-term (more than 12 months) at Define; Admissions (hospital and A&E/urgent care) short-term (less than 3 months) at Define; Admissions (hospital and A&E/urgent care) medium-term (3 to 12 months) at Define; Admissions (hospital and A&E/urgent care) long-term (more than 12 months) at Define; GP visits short-term (less than 3 months) at Define; GP visits medium-term (3 to 12 months) at Define; GP visits long-term (more than 12 months) at Define; Total adverse events (more than 12 months) at Define

Study	**Dalbeth 2012[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in New Zealand; Setting: Patients were recruited from rheumatology clinics and by public advertisement in Auckland, New Zealand from July 2009 to June 2010 (final study visit October 2010).
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of gout according to the American College of Rheumatology diagnostic classification
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients were aged ≥18 years old, had a diagnosis of gout (according to the American College of Rheumatology diagnostic classification) and were experiencing frequent gout flares at the time of study enrolment (at least two flares in the preceding 4 months).

Exclusion criteria	Lactose intolerance and severe renal impairment (estimated glomerular filtration rate (eGFR) <30 ml/min). One hundred and thirty-one patients were screened.
Age, gender and ethnicity	Age - Mean (SD): Lactose group: 56 (17), SMP: 56 (12), SMP/GMP/G600: 56 (13). Gender (M:F): 108/12. Ethnicity: Caucasian: Lactose group 70%, SMP 70% , SMP/GMP/G600 55%
Further population details	1. BMI: Not stated / Unclear 2. CKD stage: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Lactose powder. Each intervention was a cream-coloured powder administered daily as a 250 ml vanilla flavoured shake mixed in water by the patient using a wand blender. The lactose content of the lactose powder control was chosen to parallel the amount found in the SMP study products. Duration 3 months. Concurrent medication/care: Qualifying participants entered a 1-month run-in phase during which all completed a gout flare diary. Those returning a completed diary proceeded to randomisation. Medication use at baseline, n(%): allopurinol 21 (53%), colchicine 12 (30%), prednisolone 4 (10%), NSAID 11 (28%), diuretic 2 (5%). Indirectness: No indirectness. Further details: 1. Setting: Not applicable (tertiary medical centre). (n=40) Intervention 2: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Skim milk powder (SMP). The amount of SMP used in the SMP formulations was adjusted to give a total protein content of 15 g. Duration 3 months. Concurrent medication/care: Qualifying participants entered a 1-month run-in phase during which all completed a gout flare diary. Those returning a completed diary proceeded to randomisation. Medication use at baseline: allopurinol 22(55%), colchicine 7 (18%), prednisolone 8 (20%), NSAID 10(25%), diuretic 1 (2.5%). Indirectness: No indirectness. Further details: 1. Setting: Not applicable (Tertiary medical centre). (n=40) Intervention 3: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Skim milk powder (SMP) enriched with glycomacropeptide (GMP) and milk fat extract (G600) (1.5 g GMP protein (10% total protein) and 0.525 g G600 (3.5% of total protein weight)). Duration 3 months. Concurrent medication/care: Qualifying participants entered a 1-month run-in phase during which all completed a gout flare diary. Those returning a completed diary proceeded to randomisation.

	Medication use at baseline: allopurinol 22 (55%), colchicine 13 (33%), prednisolone 4 (10%), NSAID 11 (28%), diuretic 8 (20%). Indirectness: No indirectness. Further details: 1. Setting: Not applicable (Tertiary medical centre).
Funding	Study funded by industry (Funding was provided by LactoPharma (a joint venture between Fonterram Ltd, Fonterra R&D Ltd and Auckland UniServices Ltd) and the New Zealand Government Foundation for Research Science and Technology.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C versus DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C

Protocol outcome 1: Total adverse events (3 to 12 months)
- Actual outcome: total adverse events at 3 months; Group 1: 19/40, Group 2: 20/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C versus DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C

Protocol outcome 1: Total adverse events (3 to 12 months) - Actual outcome: total adverse events at 3 months; Group 1: 19/40, Group 2: 19/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0 ; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C versus DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C

Protocol outcome 1: Total adverse events (3 to 12 months)
- Actual outcome: total adverse events at 3 months; Group 1: 20/40, Group 2: 19/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in short-term medium-term (3 to 12 months); Pain in short-term and long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation in medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in medium-term (3 to 12 months; Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success short-term (less than three months); Patient global assessment of treatment success medium-term (3 to 12 months); Patient global assessment of treatment success long-term (more than 12 months); Proportion of participants who reach serum urate target level short-term (less than 3 months); Proportion of participants who reach serum urate target level in medium-term (3 to 12 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi in short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study	**Holland 2015[14]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Australia; Setting: Patients were recruited from the outpatient departments of the Royal prince Alfred and Concord Repatriation General Hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American college of rheumatology criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Males and females aged >18 years with history of gout as per American College of Rheumatology criteria, who were on stable dose of urate lowering therapy at target (serum urate <0.36 mmol/L), were included in the study
Exclusion criteria	Patients were excluded from the study if they were unable to communicate in English (both verbal and written, to standardise information)
Age, gender and ethnicity	Age - Median (range): Intervention group 64 (44-80), Control group 61 (38-77). Gender (M:F): 27/2. Ethnicity: not reported
Further population details	1. BMI: BMI 25 or over (overweight) (intervention 29 (23 - 35), 30 (24 - 37)). 2. CKD stage: Mixed population (people with CKD and people without CKD) (CKD: intervention group 5 (33%), control group 5(33%)).
Indirectness of population	No indirectness

Interventions	(n=14) Intervention 1: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. Comprehensive dietary advice. In addition to the advice given to control group, the intervention group received dietary advice in line with British Society for Rheumatology guidelines for the management of gout. the advice recommended: (1) reducing red meat intake, and avoiding offal, shellfish and yeast extract; and (2) including low fat dairy products, vegetables and cherries and the potential benefit of coffee and vitamin C. Duration 6 months. Concurrent medication/care: Allopurinol dose, mean (range) (mg) - 415 (200-900)mg. Indirectness: No indirectness Further details: 1. Setting: Hospital/secondary (secondary). (n=15) Intervention 2: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. The control group received advice regarding the importance of compliance with drug therapy, the benefit of weight loss and exercise (achieve ideal body weight) and the benefit of reduced alcohol intake. They were also advised on target urate concentration. Duration 6 months. Concurrent medication/care: Allopurinol dose at baseline, mean (range) (mg) - 525 (100-900). Indirectness: No indirectness. Further details: 1. Setting: Hospital/secondary (secondary).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES versus CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES

Protocol outcome 1: Frequency of flares in medium-term (3 to 12 months)
- Actual outcome: Flares at 6 months; Group 1: 2/14, Group 2: 1/15
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - study reports that one patient was excluded during the study due to development of tumour lysis and two dropped out. unclear how many missing in each group. study also states that 30 patients were randomised however baseline details are only reported for 29 patients; Indirectness of outcome: No indirectness; Group 1 Number missing: unclear; Group 2 Number missing: unclear

Protocol outcome 2: Proportion of participants who reach serum urate target level in medium-term (3 to 12 months)
- Actual outcome: Serum urate level (change score) at 6 months; Group 1: mean 0.3 mmol/L (SD 0.08); n=14, Group 2: mean 0.27 mmol/L (SD 0.07); n=15
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - study reports that one patient was excluded during the study due to development of tumour lysis and two dropped out. unclear how many missing in each group. study also states that 30 patients were randomised however baseline details are only reported for 29 patients; Indirectness of outcome: No indirectness; Group 1 Number missing: unclear; Group 2 Number missing: unclear

Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in short-term medium-term (3 to 12 months); Pain in short-term and long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months; Joint swelling/inflammation in medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in medium-term (3 to 12 months); Patient global assessment of treatment success in long-term (more than 12 months); Proportion of participants who reach serum urate target level in short-term (less than 3 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi in short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); Total adverse events (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study	**Juraschek 2021[17]**
Study type	RCT (Patient randomised; Crossover)

Number of studies (number of participants)	RCT (Patient randomised; Crossover)
Countries and setting	1 (n=43)
Line of therapy	Conducted in USA; Setting: primary care
Duration of study	Not applicable
Method of assessment of guideline condition	Intervention + follow up: 4 weeks
Stratum	Adequate method of assessment/diagnosis
Subgroup analysis within study	Overall
Inclusion criteria	Eligible participants were community-dwelling adults, aged ≥18 years, with a self-reported diagnosis of gout and a SU concentration ≥7 mg/dL. Gout was based on self-report in response to the question "Has a physician told you that you have gout?"
Exclusion criteria	Exclusion criteria included: active use of or plans for urate lowering therapy, excessive alcohol use, stage 4 or 5 chronic kidney disease, unstable medication use (steroid, lipid-lowering, or antihypertensive agents), active prescriptions of warfarin or insulin, major gastrointestinal conditions affecting food absorption, or inability to store food at home
Recruitment/selection of patients	Participants were recruited by identifying patients with a diagnosis of gout in the Johns Hopkins Medicine medical record, newspaper advertisements, Facebook advertisements, and mass mailings to adults living in the communities surrounding the research centre. After completion of two in-person visits at the Johns Hopkins ProHealth Clinical Research Unit (Woodlawn, Maryland, US.
Age, gender and ethnicity	Age - Mean (SD): 59/12.1. Gender (M/F): 35/8. Ethnicity: Not reported
Further population details	1. BMI: BMI 30 or over (obese) (33.5 (6.8)). 2. CKD stage: Mixed population (people with CKD and people without CKD) (eGFR, mL/min 1.73 mm2 = 78.7(16.1)).
Indirectness of population	No indirectness

Interventions	(n=22) Intervention 1: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. Dietitian directed DASH groceries - During the DDG intervention, participants participated in a one-on-one session with a dietitian at the initiation of the intervention, followed by weekly phone calls thereafter. The educational content of these sessions was restricted to instructions to eat the study foods and avoid non-study foods During the DDG assignment, participants were allotted a stipend of $105/week for the purchase of food (i.e., $15/day). We primarily used Amazon Fresh (Seattle, Washington, USA) to order and deliver foods to the ProHealth research centre for weekly pick-up by the participant. DASH diet 5–7 servings/day of grains, 4 servings/day of fruit, 4 servings/day of vegetables, 1–2 servings/day of lean meat (poultry/fish), 2 servings/day of low fat dairy, and <0.5 servings/day of high fibre foods (nuts, seeds, legumes). During the DDG period, participants were also asked to restrict alcohol, sugar-sweetened beverages (no soda, no juice), sweets, red meat, organ meats, and shellfish. Food orders were selected to be low in fat, saturated fat, and cholesterol, consistent with the original DASH diet. We also focused on groceries consistent with consuming less than 2300 mg of sodium a day. Duration 4 weeks. Concurrent medication/care: Diuretic use 27 %, losartan use 18%, Colchicine use 14%, NSAID's 14%. Indirectness: No indirectness. Further details: 1. Setting: Primary/community (n=21) Intervention 2: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. Self-directed groceries. Duration 4 weeks. Concurrent medication/care: Diuretic use 29 %, losartan use 24%, Colchicine use 19%, NSAID's 14%. Indirectness: No indirectness. Further details: 1. Setting: Primary/community (n=22) Intervention 3: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. Dietitian directed DASH groceries/Self-directed groceries - During the DDG intervention, participants participated in a one-on-one session with a dietitian at the initiation of the intervention, followed by weekly phone calls thereafter. The educational content of these sessions was restricted to instructions to eat the study foods and avoid non-study foods During the DDG assignment, participants were allotted a stipend of $105/week for the purchase of food (i.e., $15/day). We primarily used Amazon Fresh (Seattle, Washington, USA) to order and deliver foods to the ProHealth research centre for weekly pick-up by the participant. DASH diet 5–7 servings/day of grains, 4 servings/day of fruit, 4 servings/day of vegetables, 1–2 servings/day of lean meat (poultry/fish), 2 servings/day of low fat dairy, and <0.5 servings/day of high-fibre foods (nuts, seeds, legumes). During the DDG period, participants were also asked to restrict alcohol, sugar-sweetened beverages (no soda, no juice), sweets, red meat, organ meats, and shellfish. Food orders were selected to be low in fat, saturated fat, and cholesterol, consistent with the original DASH diet. We also focused on groceries consistent with consuming less than 2300 mg of sodium a day. After 4 weeks patients crossed over to self-directed groceries. Duration 8 weeks. Concurrent medication/care: Period 1 - Diuretic use 27 %, losartan use 18%, Colchicine use 14%, NSAID's 14%. period 2 not stated. Indirectness: No indirectness Further details: 1. Setting: Primary/community (n=21) Intervention 4: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based

	on gout management guidelines. Self-directed groceries/Dietitian directed DASH groceries - after 4 weeks on self-directed groceries patients crossed over dietitian-directed groceries. During the DDG intervention, participants participated in a one-on-one session with a dietitian at the initiation of the intervention, followed by weekly phone calls thereafter. The educational content of these sessions was restricted to instructions to eat the study foods and avoid non-study foods During the DDG assignment, participants were allotted a stipend of $105/week for the purchase of food (i.e., $15/day). We primarily used Amazon Fresh (Seattle, Washington, USA) to order and deliver foods to the ProHealth research centre for weekly pick-up by the participant. DASH diet 5–7 servings/day of grains, 4 servings/day of fruit, 4 servings/day of vegetables, 1–2 servings/day of lean meat (poultry/fish), 2 servings/day of low fat dairy, and <0.5 servings/day of high fibre foods (nuts, seeds, legumes). During the DDG period, participants were also asked to restrict alcohol, sugar-sweetened beverages (no soda, no juice), sweets, red meat, organ meats, and shellfish. Food orders were selected to be low in fat, saturated fat, and cholesterol, consistent with the original DASH diet. We also focused on groceries consistent with consuming less than 2300 mg of sodium a day. Duration 8 weeks. Concurrent medication/care: Period 1: Diuretic use 29 %, losartan use 24%, Colchicine use 19%, NSAID's 14% Period 2 not reported. Indirectness: No indirectness Further details: 1. Setting: Primary/community Interventions 3 and 4 were not included as it was a cross-over study with no wash-out period, therefore there could be carry over from the previous interventions.
Funding	Academic or government funding (S.P.J. is supported by a NIH/NHLBI K23HL135273. DIGO was supported by a grant from the Rheumatology Research Foundation. K. A. Carson's work on the project was funded by the Johns Hopkins Institute for Clinical and Translational Research, under grant number UL1 TR003098 from the National Centre for Advancing Translational Sciences, a component of the National Institutes of Health (NIH) and the NIH Roadmap for Medical Research. HKC is supported by NIH grant P50AR060772

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES versus CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES

Protocol outcome 1: Proportion of participants who reach serum urate target level short-term (less than 3 months)

- Actual outcome: Serum urate level, change from baseline at 4 weeks; Group 1: mean -0.55 mg/dL (SD 1.16); n=22, Group 2: mean 0 mg/dL (SD 1.03); n=21

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES versus CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES

Protocol outcome 1: Proportion of participants who reach serum urate target level short-term (less than 3 months)

- Actual outcome: Serum urate level, change from baseline at 8 weeks; Group 1: mean -0.48 mg/dL (SD 1.18); n=22, Group 2: mean -0.05 mg/dL (SD 1.01); n=21

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in short-term and medium-term (3 to 12 months); Pain in short-term and long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in medium-term (3 to 12 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in medium-term (3 to 12 months); Patient global assessment of treatment success in long-term (more than 12 months); Proportion of participants who reach serum urate target level in medium-term (3 to 12 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); Total adverse events (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study (subsidiary papers)	**Schlesinger 2012[31]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in USA; Setting: Unclear/not stated
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: MSU crystal- proven gout
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eighteen patients with MSU crystal- proven gout were entered into this study.
Exclusion criteria	Not stated
Age, gender and ethnicity	Age - Median (range): 56.43 (28-75). Gender (M:F): not reported. Ethnicity: Caucasian 11, Asian 1, Hispanic 1, African American 1
Further population details	1. BMI: BMI 30 or over (obese) (mean (SE) - 30.02(0.84). 2. CKD stage: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Cherry juice - patients received a tablespoon of cherry juice concentrate twice daily. Duration 4 months. Concurrent medication/care: 3 of 9 patients (33%) were taking allopurinol

	(100-500 mg daily). Five patients (55%) in group A taking NSAIDs chronically (Celcoxib n=3; indomethacin n=2) discontinued NSAIDs within 60 days of starting cherry juice. Indirectness: No indirectness Further details: 1. Setting: Not stated / Unclear (n=5) Intervention 2: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Pomegranate juice - patients received a tablespoon of pomegranate juice concentrate twice daily. Duration 4 months. Concurrent medication/care: 2 of 5 patients were taking allopurinol (100-500 mg daily). Indirectness: No indirectness Further details: 1. Setting: Not stated / Unclear
Funding	Equipment / drugs provided by industry (The prospective RCT was supported by a grant from Brownwood Acres Foods.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C versus DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C

Protocol outcome 1: Frequency of flares medium-term (3 to 12 months)
- Actual outcome: Flares - number of flares at 4 months; Group 1: 7/9, Group 2: 6/5
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Flares - number of people with at least 1 gout flare at 4 months; Group 1: 4/9, Group 2: 4/5
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcome 2: Proportion of participants who reach serum urate target level medium-term (3 to 12 months)
- Actual outcome: serum urate level (mg/dL) at 4 months; Group 1: mean 8.17 mg/dL (SD 3.3); n=9, Group 2: mean 6.14 mg/dL (SD 2.39); n=5
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in short-term and medium-term (3 to 12 months); Pain in short-term and long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation in medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in

	long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in medium-term (3 to 12 months); Patient global assessment of treatment success in long-term (more than 12 months; Proportion of participants who reach serum urate target level in short-term (less than 3 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi in short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); Total adverse events (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study (subsidiary papers)	**Singh 2019[32] (Singh 2020[33])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 9 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: patient self-reported physician diagnosis of gout
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) US adults aged 18 years or older; (2) a valid US mailing address and e-mail address; (3) patient self-reported physician diagnosis of gout.
Exclusion criteria	Self-reported presence of other types of inflammatory arthritis including rheumatoid arthritis or spondyloarthritis and the current use of cherry extract, juice, or concentrate.
Age, gender and ethnicity	Age - Mean (SD): Cherry extract group: 58.2 (15.5), Diet modification group: 53.6 (11.9). Gender (M:F): 61/23. Ethnicity: Cherry extract group: White 30 (73%), Black or African American 9 (22%), Asian/other/mixed 2 (5%); Diet modification group. White 27 (63%), Black or African American 12 (28%), Asian/other/mixed 4 (9%);
Further population details	1. BMI: Not stated / Unclear 2. CKD stage : Not stated / Unclear

Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. Cherry extract 3,600 mg daily (3 capsules of 1200 mg each daily, each equivalent to 32 oz of cherry juice or a pound of cherries. Patients were sent the 3-month supply of cherry capsules, to each study participant at 3, 6, and 9 months, supplemented with study coordinator calls to encourage cherry extract adherence. Receipt was confirmed via e-mail or phone conversation. Duration 9 months. Concurrent medication/care: Taking allopurinol, febuxostat or probenecid at baseline 13 (33%). Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=43) Intervention 2: Dietary modifications - Change in dietary patterns e.g. DASH, Mediterranean diets, dietary pattern based on gout management guidelines. Diet modification. Patients were sent individualized diet recommendation (based on baseline FFQ data) to each study participant at 3, 6, and 9 months, supplemented with dietitian calls to discuss specific recommendations. Receipt was confirmed via e-mail or phone conversation. Duration 9 months. Concurrent medication/care: Taking allopurinol, febuxostat or probenecid at baseline 17(42%). Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear
Funding	Academic or government funding (This study was funded by an intramural grant from the University of Alabama at Birmingham Centre for Outcomes and Effectiveness Research and Education/Minority Health Research Centre (principal investigator, J.A.S.) and an intramural grant from the University of Alabama at Birmingham Centre for Clinical and Translational Studies (principal investigator, J.A.S.). The funding body did not play any role in the design, collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY SUPPLEMENTATION E.G. ENRICHED SKIMMED MILK POWDER, CHERRY EXTRACT/CONCENTRATE, OMEGA-3 POLYUNSATURATED FATTY ACIDS, VITAMIN C versus CHANGE IN DIETARY PATTERNS E.G. DASH, MEDITERRANEAN DIETS, DIETARY PATTERN BASED ON GOUT MANAGEMENT GUIDELINES

Protocol outcome 1: Pain short-term in medium-term (3 to 12 months)
- Actual outcome: Pain - average pain score over 24 hours at 9 months; Group 1: mean 0.84 (SD 1.44); n=32, Group 2: mean 0.85 (SD 1.69); n=26
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 7

Protocol outcome 2: Frequency of flares medium-term (3 to 12 months)

	- Actual outcome: Flares (proportion with any gout flare patient reported) at 9 months; Group 1: 23/41, Group 2: 28/43 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Patient global assessment of treatment success medium-term (3 to 12 months) - Actual outcome: HAQ-DI. (Health assessment questionnaire-disability index) at 9 months; Group 1: mean 0.28 (SD 0.54); n=41, Group 2: mean 0.23 (SD 0.4); n=42; Comments: 0-1 mild to moderate disability; 1-2 moderate to severe disability; 2-3 severe to very severe disability. Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Proportion of participants who reach serum urate target level medium-term (3 to 12 months) - Actual outcome: Serum urate level at 9 months; Group 1: mean 7.16 mg/dL (SD 1.71); n=41, Group 2: mean 7 mg/dL (SD 1.91); n=43 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Number of patients achieving sUA <6mg/dL at 9 months; Group 1: 7/34, Group 2: 8/31 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 12 - Actual outcome: Number of patients achieving sUA <5mg/dL at 9 months; Group 1: 2/34, Group 2: 5/31 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 12 Protocol outcome 5: Total adverse events (3 to 12 months) - Actual outcome: AE - Any adverse events at 9 months; Group 1: 1/32, Group 2: 0/26; Comments: reported as a percentage Cherry group 3.1 % N=32; Diet group 0.0% N=26. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9; Group 2 Number missing: 7 - Actual outcome: AE - specific gastrointestinal adverse events at 9 months; Group 1: 9/32, Group 2: 7/26; Comments: reported as a percentage Cherry group 28.1 % N=32; Diet group 26.9% N=26 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 7
Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain short-term Long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation in medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint

	tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in long-term (more than 12 months); Proportion of participants who reach serum urate target level in short-term (less than 3 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi in short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study	**Stamp 2013[35]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in New Zealand; Setting: Unclear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American College of Rheumatology preliminary criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with gout, whose diagnosis was defined according to the American College of Rheumatology preliminary criteria and with an SU level >0.36 mmoles/liter (6 mg/dl) were recruited.
Exclusion criteria	Patients taking over-the-counter vitamin supplements were excluded
Age, gender and ethnicity	Age - Mean (range): Vit C group - 61.2(39-86), no vitamin C - 55(27 - 78). Gender (M:F): 36/4. Ethnicity: New Zealand European 15 (37.5%), Other 25(62.5%)
Further population details	1. BMI: BMI 30 or over (obese) (vitamin C (30.4(0.96), no vitamin C 32(1.5)). 2. CKD stage : People with CKD (stages 1-2)
Extra comments	None
Indirectness of population	No indirectness

Interventions	(n=10) Intervention 1: Dietary modifications - Increased intake of; coffee, dairy or vitamin C (dietary and supplementary) omega-3, Polyunsaturated Fatty Acids, rich fish, cherries, tomatoes, water. Vitamin C 500 mg per day (in patients not taking allopurinol at baseline). Duration 2 months. Concurrent medication/care: Patients not taking allopurinol at baseline. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 2: Urate-lowering medications - xanthine oxidase inhibitors. Allopurinol up to 100mg per day. Allopurinol was started at 50mg or 100mg (in patients not taking allopurinol at baseline). Duration 2 months. Concurrent medication/care: Patients not taking allopurinol at baseline. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 3: Dietary modifications - Increased intake of; coffee, dairy or vitamin C (dietary and supplementary)omega-3, Polyunsaturated Fatty Acids, rich fish, cherries, tomatoes, water. Vitamin C at a dosage of 500 mg/day (in patients already taking allopurinol at baseline). Duration 2 months. Concurrent medication/care: Patients already taking allopurinol at baseline. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 4: Urate-lowering medications - xanthine oxidase inhibitors. Allopurinol increased dose. Allopurinol was increased by 50 mg or 100mg increments, at the discretion of the physician, depending on each patient's renal function and comorbidities. The dose of allopurinol was further increased at 4 weeks if the patient had not achieved the target SU level of <0.36 mmoles/litre (6mg/dl). Duration 2 months. Concurrent medication/care: Patients already taking allopurinol at baseline. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear
Funding	Academic or government funding (Supported by the Health Research Council of New Zealand)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED INTAKE OF; COFFEE, DAIRY OR VITAMIN C (DIETARY AND SUPPLEMENTARY) OMEGA-3, POLYUNSATURATED FATTY ACIDS, RICH FISH, CHERRIES, TOMATOES, WATER versus XANTHINE OXIDASE INHIBITORS

Protocol outcome 1: Proportion of participants who reach serum urate target level short-term (less than 3 months)
- Actual outcome: Serum urate level (in people not taking allopurinol at baseline) at 2 months; Group 1: mean -0.07 (SD 1.26); n=10, Group 2: mean -2.5 (SD 1.26); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED INTAKE OF; COFFEE, DAIRY OR VITAMIN C (DIETARY AND SUPPLEMENTARY) OMEGA-3, POLYUNSATURATED FATTY ACIDS, RICH FISH, CHERRIES, TOMATOES, WATER. versus XANTHINE OXIDASE INHIBITORS

Protocol outcome 1: Proportion of participants who reach serum urate target level short-term (less than 3 months) - Actual outcome: Serum urate level (in people already taking allopurinol at baseline) at 2 months; Group 1: mean -0.5 (SD 1.26); n=10, Group 2: mean -1.5 (SD 1.26); n=10 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in medium-term (3 to 12 months); Pain in long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in short-term (less than 3 months); Frequency of flares in medium-term (3 to 12 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in medium-term (3 to 12 months); Patient global assessment of treatment success in long-term (more than 12 months); Proportion of participants who reach serum urate target level in medium-term (3 to 12 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi in short-term (less than 3 months); Total adverse events (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in short-term (less than 3 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) in long-term (more than 12 months); GP visits in short-term (less than 3 months); GP visits in medium-term (3 to 12 months); Total adverse events (3 to 12 months); GP visits in long-term (more than 12 months); Total adverse events (more than 12 months)

Study	**Stamp 2020[34]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in New Zealand; Setting: Not reported.

Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with gout as defined by the ARA preliminary classification criteria for gout with a SU of >0.36 mmol/l (6 mg/dl) were recruited.
Exclusion criteria	People with type 1 diabetes and those receiving diuretics were excluded.
Recruitment/selection of patients	Recruitment was selective to ensure half the participants were receiving allopurinol and half were on no ULT.
Age, gender and ethnicity	Age - Mean (SD): Placebo group: 56.9(12.9) 7.5ml group: 63.3 (13.0), 15ml group: 61.0 (9), 22.5ml group: 56.2 (11.4), 30ml group: 60.4 (11.6). Gender (M:F): Placebo group: 9M/1F 7.5ml group: 9M/1F, 15ml group: 9M/1F, 22.5ml group: 8M/2F, 30ml group: 10M/0F. Ethnicity: Placebo group: NZ European 4, Maori/ Pacific 6; 7.5ml group: NZ European 9, Maori/ Pacific 1 15ml group: NZ European 7, Maori/ Pacific 3; 22.5ml group: NZ European 7, Maori/ Pacific 3; 30ml group: NZ European 8, Maori/ Pacific 2
Further population details	1. BMI: Systematic review: mixed (Placebo group: 30.5(9.2) 7.5ml group: 31.2(10.0), 15ml group: 28.8(3.7), 22.5ml group: 28.9 (3.2), 30ml group: 29.5(4.5)). 2. CKD stage : Mixed population (people with CKD and people without CKD) (Placebo group: 2, 7.5ml group: 0, 15ml group: 0, 22.5ml group: 0, 30ml group: 1).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. 7.5 ml of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with cherry concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about 15g sugar per 30 mls). Duration 28 days. Concurrent medication/care: 5 patients were taking allopurinol. Indirectness: No indirectness. Further details: 1. Setting: Not stated /

	Unclear (n=10) Intervention 2: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. 15 ml of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with Cherry Concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about 15g sugar per 30 mls). Duration 28 days. Concurrent medication/care: 5 patients were taking allopurinol. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 3: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. 22.5 ml of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with cherry concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about 15g sugar per 30 mls). Duration 28 days. Concurrent medication/care: 5 patients were taking allopurinol. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 4: Dietary modifications - Dietary supplementation e.g. enriched skimmed milk powder, cherry extract/concentrate, Omega-3 Polyunsaturated Fatty Acids, vitamin C. 30 ml of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with cherry concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about 15g sugar per 30 mls). Duration 28 days. Concurrent medication/care: 5 patients were taking allopurinol. Indirectness: No indirectness. Further details: 1. Setting: Not stated / Unclear (n=10) Intervention 5: Placebo - e.g. with some dietary supplement studies. 2 drops of tart cherry juice concentrate twice daily in 250ml water for 28 days. Participants were provided with cherry concentrate 946ml bottles, which contain juice from about 3000 Montmorency cherries (1 ml about 3 cherries) and about 15g sugar per 30 mls). Duration 28 days. Concurrent medication/care: 5 patients were taking allopurinol. Indirectness: No indirectness. Further details: 1. Setting: Not stated/Unclear
Funding	Academic or government funding (Heath Research Council of New Zealand).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 7.5ML CHERRY EXTRACT/CONCENTRATE versus PLACEBO Protocol outcome 1: Frequency of flares in short-term (less than 3 months)	

- Actual outcome: Gout flares at Day 28; Group 1: mean 0.6 (SD 0.5); n=10, Group 2: mean 0.4 (SD 0.5); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Proportion of participants who reach serum urate target level in short-term (less than 3 months)
- Actual outcome: Serum urate (mmol/l) at Day 28; Group 1: mean 0.4 (SD 0.08); n=10, Group 2: mean 0.47 (SD 0.12); n=10
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Total adverse events (less than 3 months)
- Actual outcome: Adverse events. at within the 28 day study period; Group 1: 3/10, Group 2: 6/10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Admissions (hospital and A&E/urgent care) in short-term (less than 3 months)
- Actual outcome: Serious adverse events (Hospital admission with a condition deemed unrelated to study medication.) at within the 28 day study period; Group 1: 2/10, Group 2: 0/10; Comments: 1 patient was admitted to hospital after requiring surgery for a strangulated hernia on day 7. 1 patient was admitted to hospital with an exacerbation of heart failure on day 21. Possible double counting with the adverse events outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 15ML CHERRY EXTRACT/CONCENTRATE versus PLACEBO

Protocol outcome 1: Frequency of flares in short-term (less than 3 months)
- Actual outcome: Gout flares at Day 28; Group 1: mean 0.4 (SD 0.5); n=10, Group 2: mean 0.4 (SD 0.5); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Proportion of participants who reach serum urate target level in short-term (less than 3 months)
- Actual outcome: Serum urate (mmol/l) at Day 28; Group 1: mean 0.44 (SD 0.1); n=10, Group 2: mean 0.47 (SD 0.12); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Total adverse events (less than 3 months)
- Actual outcome: Adverse events. at within the 28 day study period; Group 1: 11/10, Group 2: 6/10; Comments: There were 24 adverse events in 24 patients during the study. The number in the cherry group appears to be incorrect.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 22.5ML CHERRY EXTRACT/CONCENTRATE versus PLACEBO

Protocol outcome 1: Frequency of flares short-term (less than 3 months)
- Actual outcome: Gout flares at Day 28; Group 1: mean 0.6 (SD 0.5); n=10, Group 2: mean 0.4 (SD 0.5); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:

Protocol outcome 2: Proportion of participants who reach serum urate target level short-term (less than 3 months)
- Actual outcome: Serum urate (mmol/l) at Day 28; Group 1: mean 0.44 (SD 0.12); n=10, Group 2: mean 0.47 (SD 0.12); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Total adverse events (less than 3 months)
- Actual outcome: Adverse events. at within the 28 day study period; Group 1: 2/10, Group 2: 2/10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 30ML CHERRY EXTRACT/CONCENTRATE versus PLACEBO

Protocol outcome 1: Frequency of flares in short-term (less than 3 months)
- Actual outcome: Gout flares at Day 28; Group 1: mean 0.4 (SD 0.5); n=10, Group 2: mean 0.4 (SD 0.5); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Proportion of participants who reach serum urate target level in short-term (less than 3 months)
- Actual outcome: Serum urate (mmol/l) at Day 28; Group 1: mean 0.42 (SD 0.08); n=10, Group 2: mean 0.47 (SD 0.12); n=10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

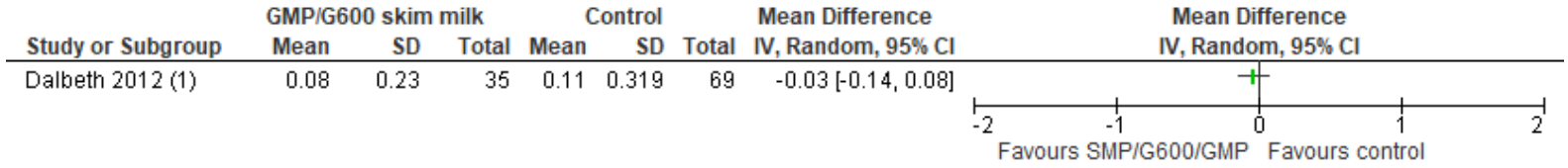
Protocol outcome 3: Total adverse events (less than 3 months)
- Actual outcome: Adverse events. at within the 28 day study period; Group 1: 2/10, Group 2: 2/10
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life in short-term (less than three months); Quality of life in medium-term (3 to 12 months); Quality of life in long-term (more than 12 months); Pain in short-term (less than 3 months); Pain in medium-term (3 to 12 months); Pain in long-term (more than 12 months); Joint swelling/inflammation in short-term (less than 3 months); Joint swelling/inflammation in medium-term (3 to 12 months); Joint swelling/inflammation in long-term (more than 12 months); Joint tenderness in short-term (less than 3 months); Joint tenderness in medium-term (3 to 12 months); Joint tenderness in long-term (more than 12 months); Frequency of flares in medium-term (3 to 12 months); Frequency of flares in long-term (more than 12 months); Patient global assessment of treatment success in short-term (less than three months); Patient global assessment of treatment success in medium-term (3 to 12 months); Patient global assessment of treatment success in long-term (more than 12 months); Proportion of participants who reach serum urate target level in medium-term (3 to 12 months); Proportion of participants who reach serum urate target level in long-term (more than 12 months); Radiographic joint damage (less than 3 months); Radiographic joint damage (3 to 12 months); Radiographic joint damage (more than 12 months); Renal stones (less than 3 months); Renal stones (3 to 12 months); Renal stones (more than 12 months); Tophi short-term (less than 3 months); Tophi in medium-term (3 to 12 months); Tophi in long-term (more than 12 months); Admissions (hospital and A&E/urgent care) in medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) long-term (more than 12 months); GP visits short-term (less than 3 months); GP visits in medium-term (3 to 12 months); Total adverse events (3 to 12 months); GP visits long-term (more than 12 months); Total adverse events (more than 12 months)

Appendix E – Forest plots

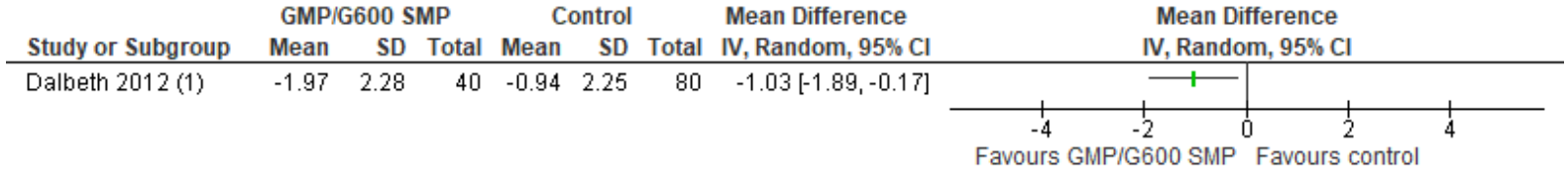
E.1 Enriched skim milk powder (SMP) (GMP/G600) versus control (SMP/lactose)

Figure 2: HAQ-II -physical function (0-3), at 3 months, better indicated by lower score



Footnotes
(1) Measured using the health assessment questionnaire (HAQ-II)

Figure 3: Pain during gout flares – change score (0-10 Likert scale), at 3 months, better indicated by lower score



Footnotes
(1) Pain measured using a 0-10 Likert scale

Figure 4: Number of gout flares per month, after 3 months, better indicated by lower score

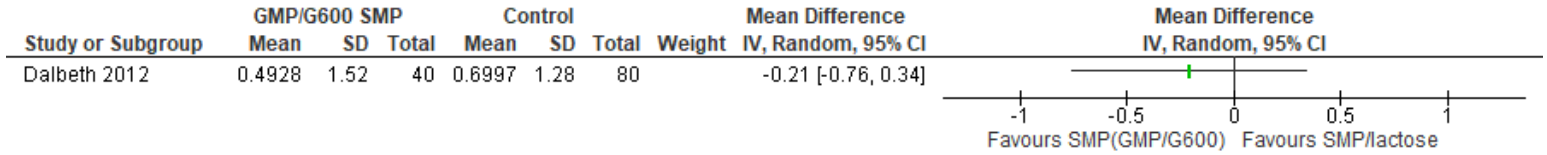


Figure 5: Total adverse events (number of patients with at least 1 adverse event), at 3 months, better indicated by lower score

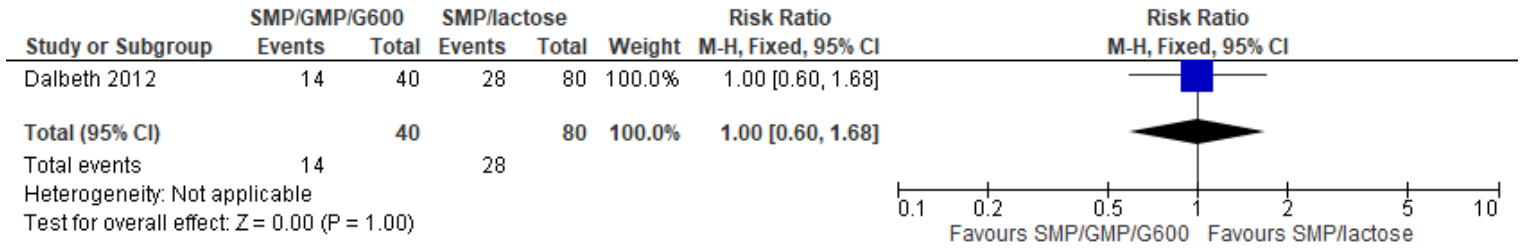
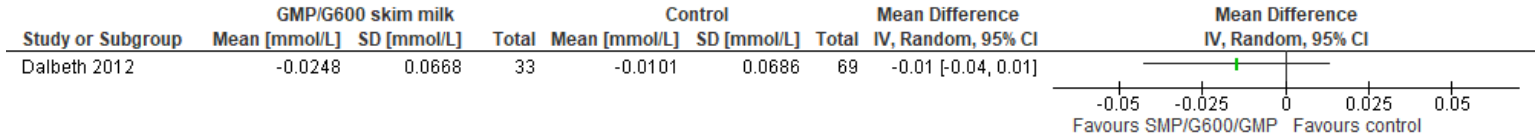
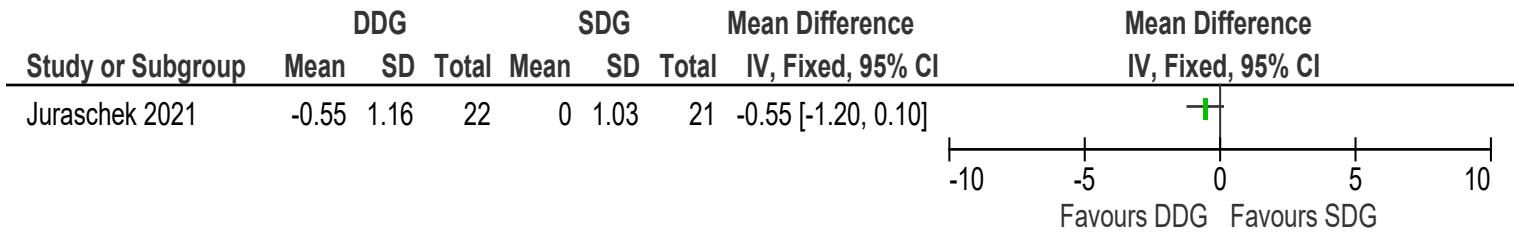


Figure 6: Serum uric acid reduction (mmol/L) (change score), at 3 months, better indicated by lower score



E.2 Dietitian directed groceries versus self-directed groceries

Figure 7: Serum urate level (change score) at 4 weeks, better indicated by lower score



E.3 Cherry extract versus individualised diet modification

Figure 8: HAQ-DI (scale 0-3) at 9 months, better indicated by lower score

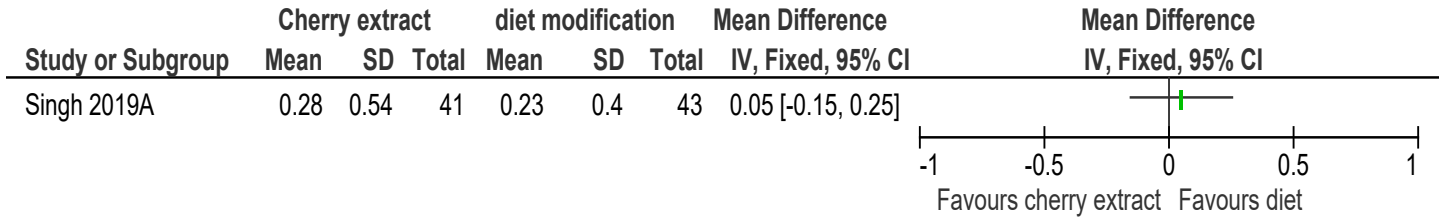


Figure 9: Average pain score (scale 0-10) at 9 months, better indicated by lower score

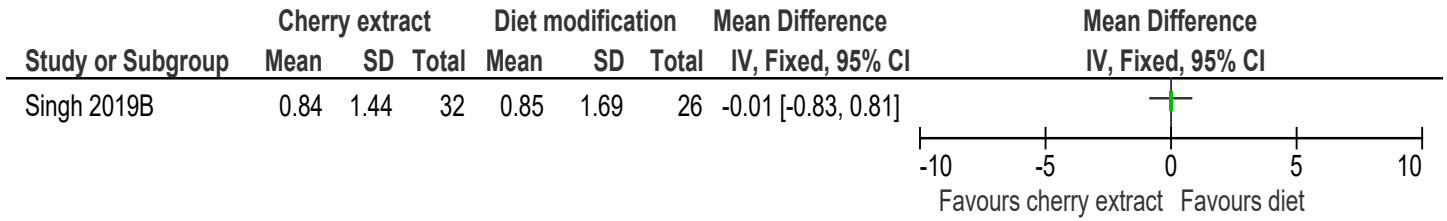


Figure 10: Number of patients with at least 1 gout flare at 9 months, better indicated by lower score

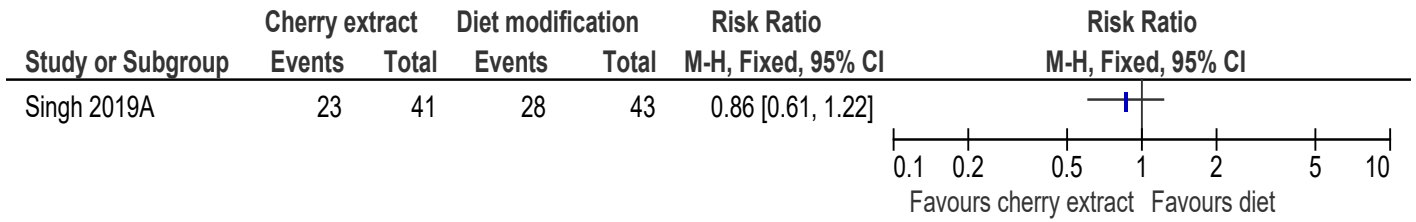


Figure 11: Any adverse event (not including gastrointestinal adverse events) at 9 months, better indicated by lower score

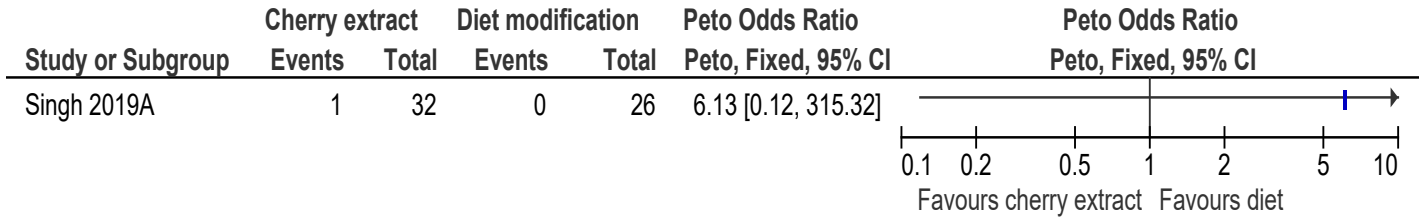


Figure 12: Specific gastrointestinal adverse events at 9 months, better indicated by lower score

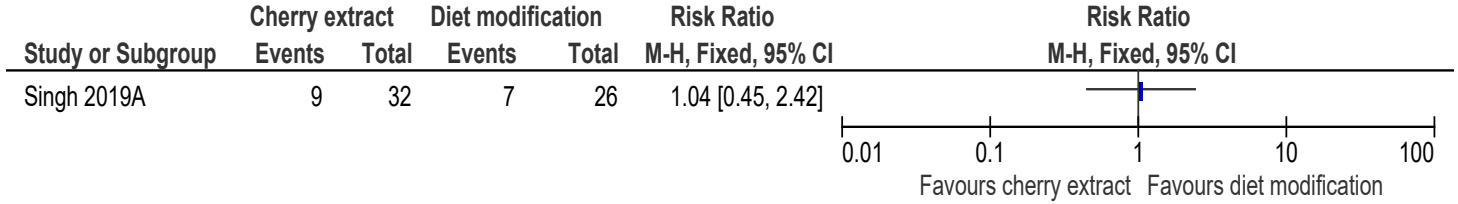


Figure 13: Serum urate level at 9 months, better indicated by lower score

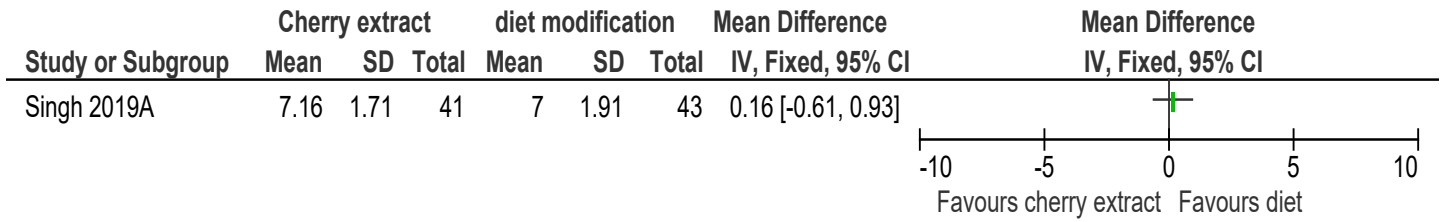


Figure 14: Number of patients achieving sUA <6mg/dL at 9 months, better indicated by higher score

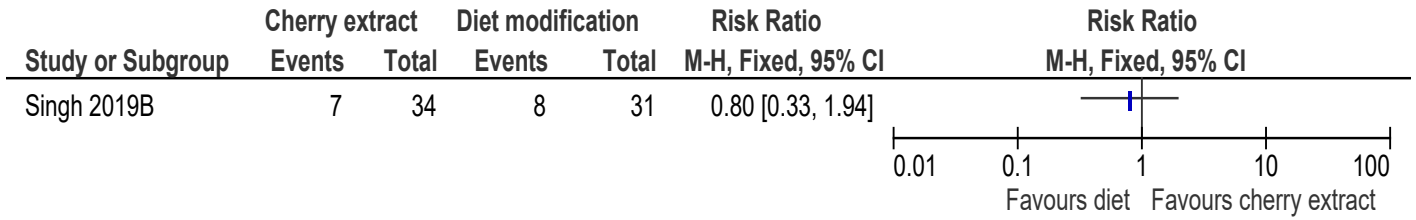
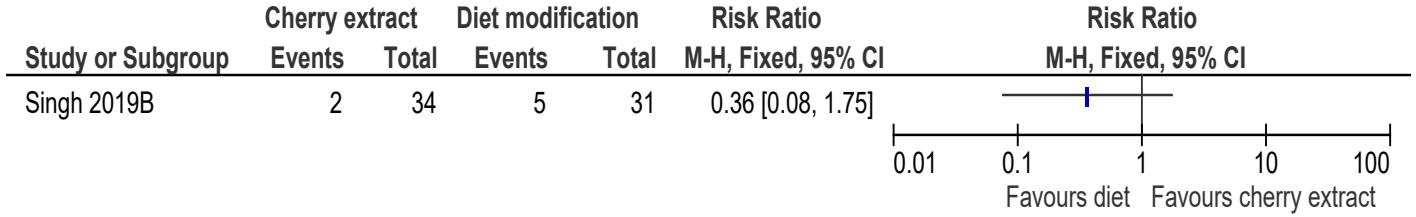


Figure 15: Number of patients achieving sUA <5mg/dL at 9 months, better indicated by higher score



E.4 Cherry juice concentrate versus pomegranate juice concentrate

Figure 16: Number of people with at least 1 gout flare at 4 months, better indicated by lower score

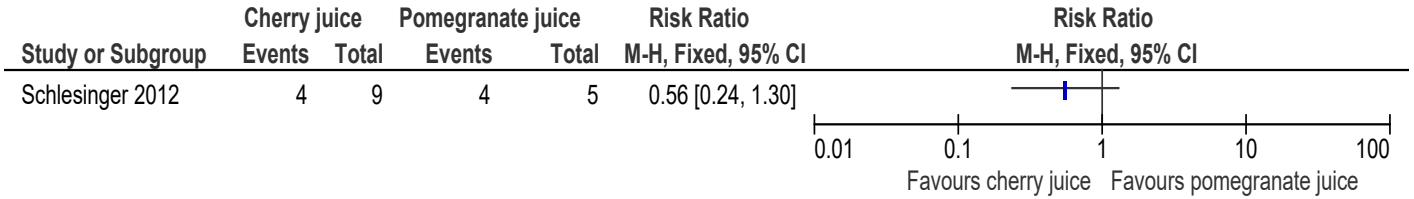
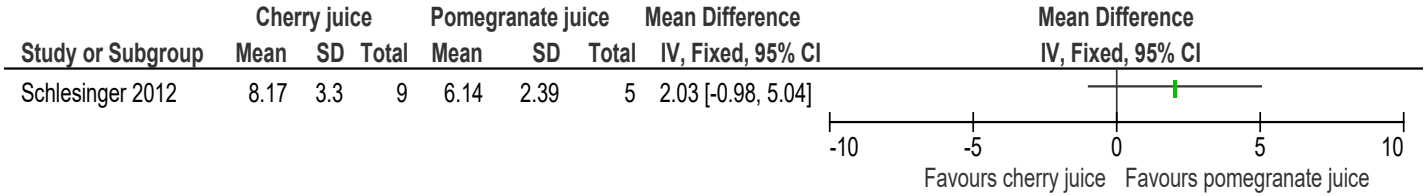


Figure 17: Serum urate level at 4 months, better indicated by lower score



E.5 Comprehensive dietary advice versus basic dietary advice

Figure 18: Total number of flares at 6 months (better indicated by lower)

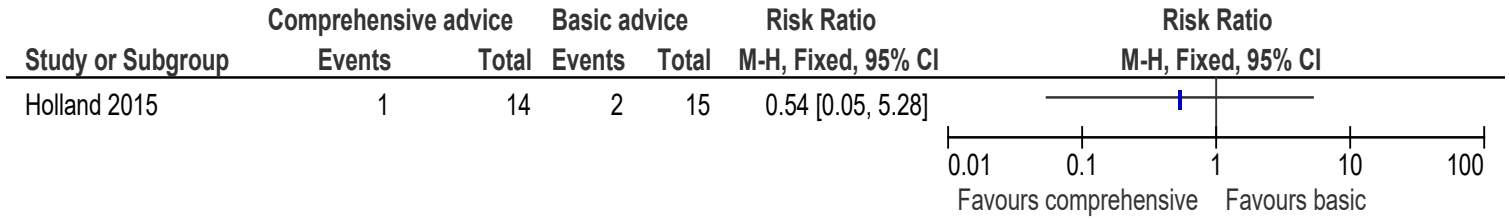
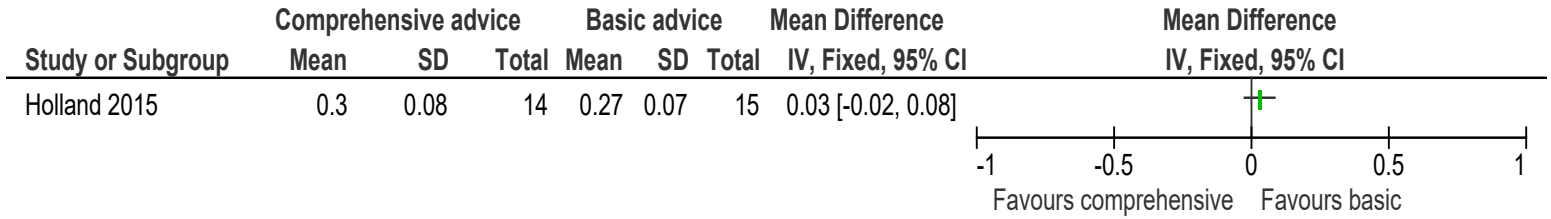
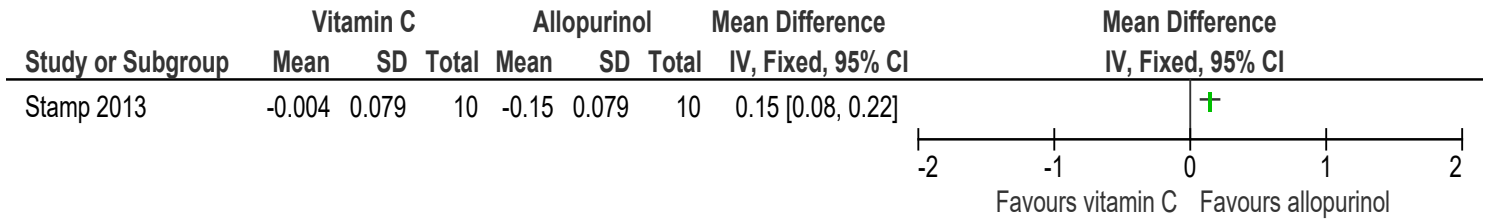


Figure 19: Serum urate level at 6 months, (mmol/L) (change scores) better indicated by lower score



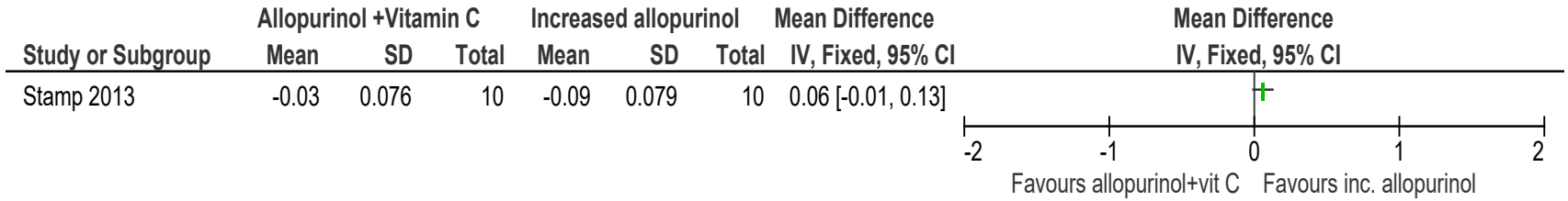
E.6 Vitamin C versus allopurinol (in people not taking allopurinol at baseline)

Figure 20: Serum urate level, change score (mmol/L) at 8 weeks, better indicated by lower score



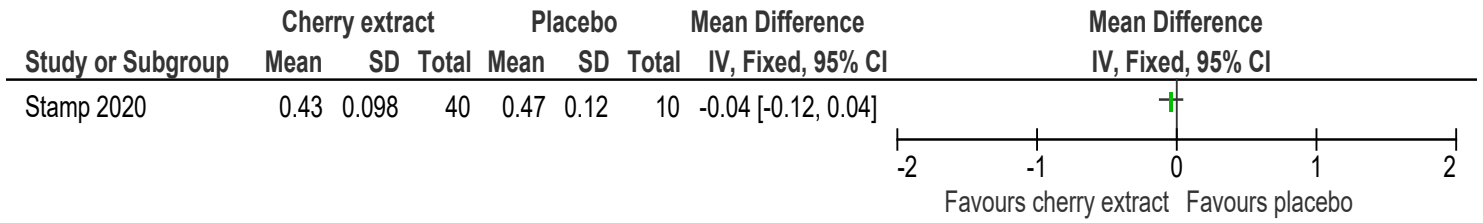
E.7 Allopurinol and vitamin C versus increased dose of allopurinol (in people taking allopurinol at baseline)

Figure 21: Serum urate level, change score at 8 weeks, better indicated by lower score



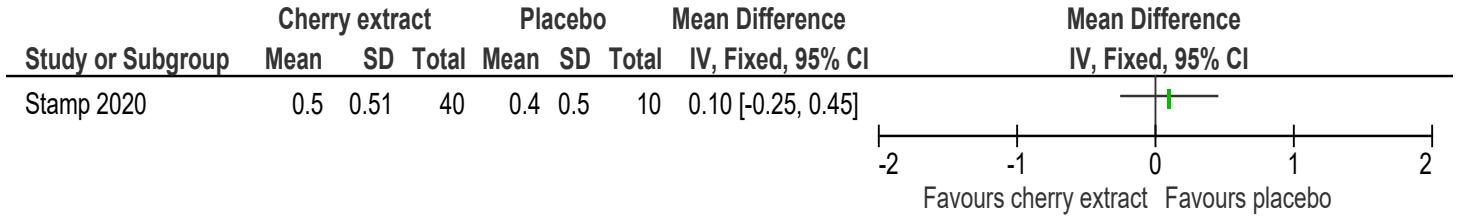
E. 9 Cherry extract versus placebo (in people taking and not taking allopurinol at baseline)

Figure 23: Serum urate level at 28 days, better indicated by lower score



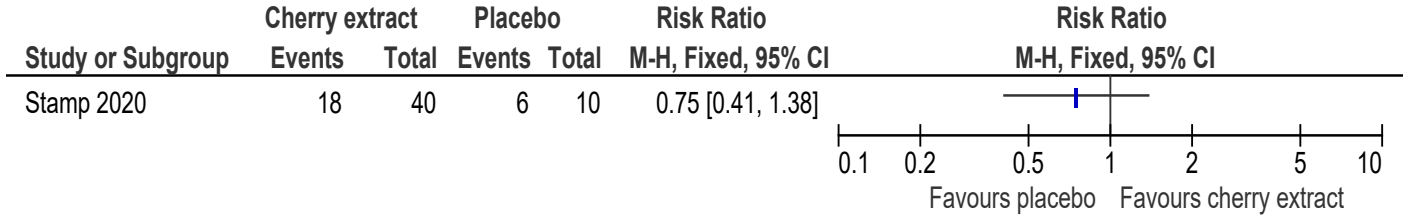
Results for the 4 cherry extract groups were combined for analysis

Figure 24: Number of gout flares at 28 days, better indicated by lower score



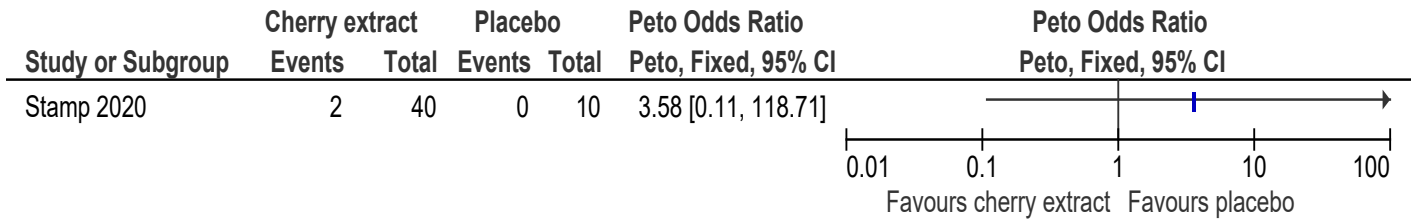
Results for the 4 cherry extract groups were combined for analysis

Figure 25: Number of people with adverse events, at 28 days (better indicated by lower)



Results for the 4 cherry extract groups were combined for analysis

Figure 26: Number of hospital admissions (serious adverse events), at 28 days (better indicated by lower)



Results for the 4 cherry extract groups were combined for analysis

Appendix F – GRADE

Table 13: Clinical evidence profile: enriched skim milk powder (SMP) (GMP/G600) versus control (SMP/lactose)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Skim milk powder (SMP) (GMP/G600)	control (SMP/lactose)	Relative (95% CI)	Absolute (95% CI)		
Physical function – HAQ-II (0-3 scale), better indicated by lower score												
1	randomised trials	not serious	not serious	not serious	not serious	none	35	69	-	MD **0.03 lower** (0.14 lower to 0.08 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain during gout flares (change score) (0-10 Likert Scale) at 3 months, better indicated by lower score												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	40	80	-	MD **1.03 lower** (1.89 lower to 0.17 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of gout flares per month (change score), after 3 months GMP/G600 SMP versus co (follow up: mean 3 months), better indicated by lower score												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Skim milk powder (SMP) (GMP/G600)	control (SMP/lactose)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	40	80	-	MD **0.21 lower** (0.76 lower to 0.34 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Total adverse events (number of patients with at least 1 adverse event) at 3 months, better indicated by lower score												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	14/40 (35.0%)	28/80 (35.0%)	**RR 0.95** (0.61 to 1.49)	**18 fewer per 1,000** (from 136 fewer to 172 more)	⊕⊕◯◯ LOW	CRITICAL
Serum uric acid reduction (mmol/L) t 3 months (change score), better indicated by lower score												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	33	69	-	MD **0.01 lower** (0.04 lower to 0.01 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for HAQ-II – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for pain during gout flares was 0.825.

Table 14: Clinical evidence profile: dietitian directed groceries versus self-directed groceries

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dietitian-directed Dash groceries	self-directed groceries	Relative (95% CI)	Absolute (95% CI)		
Serum urate level (mmol/L), (change score) at 4 weeks, better indicated by lower score												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	21	-	MD **0.55 lower** (1.2 lower to 0.1 higher)	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for .serum urate level was 0.38.

Table 15: Clinical evidence profile: cherry extract versus individualised diet modification

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Check this Cherry extract	individualised diet modification	Relative (95% CI)	Absolute (95% CI)		
HAQ-DI (scale 0-3) at 9 months, better indicated by lower score												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Check this Cherry extract	individualised diet modification	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	41	43	-	MD **0.05 higher** (0.15 lower to 0.25 higher)	⊕◯◯◯ VERY LOW	CRITICAL

Average pain score (0-10) in the last 24 hours at 9 months, better indicated by lower score

1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	32	26	-	MD **0.01 lower** (0.83 lower to 0.81 higher)	⊕◯◯◯ VERY LOW	CRITICAL

Proportion with any gout flare at 9 months, better indicated by lower score

1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	23/41 (56.1%)	28/43 (65.1%)	**RR 0.86** (0.61 to 1.22)	**91 fewer per 1,000** (from 254 fewer to 143 more)	⊕◯◯◯ VERY LOW	CRITICAL

Any adverse event (not including gastrointestinal adverse events) at 9 months, better indicated by lower score

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Check this Cherry extract	individualised diet modification	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/32 (3.1%)	0/26 (0.0%)	**Peto OR 6.13** (0.12 to 315.32)	**30 more per 1,000** (from 60 fewer to 120 more)	⊕◯◯◯ VERY LOW	CRITICAL

Specific gastrointestinal adverse events at 9 months, better indicated by lower score

1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/32 (28.1%)	7/26 (26.9%)	**RR 1.04** (0.45 to 2.42)	**11 more per 1,000** (from 148 fewer to 382 more)	⊕◯◯◯ VERY LOW	CRITICAL

Serum urate level at 9 months, better indicated by lower score

1	randomised trials	serious [a]	not serious	not serious	not serious	none	41	43	-	MD **0.16 higher** (0.61 lower to 0.93 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Number of patients achieving sUA <6mg/dL at 9 months, better indicated by higher score

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Check this Cherry extract	individualised diet modification	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/34 (20.6%)	8/31 (25.8%)	**RR 0.80** (0.33 to 1.94)	**52 fewer per 1,000** (from 173 fewer to 243 more)	⨁◯◯◯ VERY LOW	CRITICAL
Number of patients achieving sUA <5mg/dL at 9 months, better indicated by higher score												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/34 (5.9%)	5/31 (16.1%)	**RR 0.36** (0.08 to 1.75)	**103 fewer per 1,000** (from 148 fewer to 121 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for pain was 1.5; and for serum urate level was 0.99.

Table 16: Clinical evidence profile: cherry juice concentrate versus pomegranate juice concentrate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cherry juice concentrate	pomegranate juice	Relative (95% CI)	Absolute (95% CI)		
Flares (number of people with at least 1 flare) per 4 months, better indicated by lower score												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/9 (44.4%)	4/5 (80.0%)	**RR 0.56** (0.24 to 1.30)	**352 fewer per 1,000** (from 608 fewer to 240 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serum urate level (mg/dL) at 4 months, better indicated by lower score												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	9	5	-	MD **2.03 higher** (0.98 lower to 5.04 higher)	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; .for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. The calculated MID for serum urate level was 0.96.

Table 17: Clinical evidence profile: comprehensive dietary advice versus basic dietary advice

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comprehensive dietary advice	basic dietary advice	Relative (95% CI)	Absolute (95% CI)		
Flares at 6 months, better indicated by lower score												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/14 (7.1%)	2/15 (13.3%)	**RR 0.54** (0.05 to 5.28)	**61 fewer per 1,000** (from 127 fewer to 571 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serum urate level (mmol/L) at 6 months, better indicated by lower score												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14	15	-	MD **0.03 higher** (0.02 lower to 0.08 higher)	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. Where there was only one study 0.5 (SMD) was used for continuous outcomes.

Table 18: Clinical evidence profile: vitamin C versus allopurinol (in people not taking allopurinol at baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C supplement	allopurinol (people not taking allopurinol at baseline)	Relative (95% CI)	Absolute (95% CI)		
Serum urate level (mmol/L) at 8 weeks (change score), better indicated by lower score												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	10	10	-	MD **0.15 higher** (0.08 higher to 0.22 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes. Where there was only one study 0.5 (SMD) was used for continuous outcomes.

Table 19: Clinical evidence profile: allopurinol and vitamin C versus increased dose of allopurinol (in people taking allopurinol at baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol + vitamin C supplement	increased dose allopurinol (people taking allopurinol at baseline)	Relative (95% CI)	Absolute (95% CI)		
Serum urate level at 8 weeks (change score), better indicated by lower score												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	10	10	-	MD **0.06 higher** (0.01 lower to 0.13 higher)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used: for continuous outcomes the MID was calculated as 0.4 for serum urate level.

Table 20Clinical evidence profile: cherry extract versus placebo (in people taking and not taking allopurinol at baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cherry extract	placebo	Relative (95% CI)	Absolute (95% CI)		
Serum urate (follow up: 28 days), better indicated by lower score												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	40	10	-	MD **0.04 lower** (0.12 lower to 0.04 higher)	⨁⨁◯◯ LOW	CRITICAL
Number of gout flares (follow up: 28 days), better indicated by lower score												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	40	10	-	MD **0.1 higher** (0.25 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: 28 days), better indicated by lower score												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	18/40 (45.0%)	6/10 (60.0%)	**RR 0.75** (0.41 to 1.38)	**150 fewer per 1,000** (from 354 fewer to 228 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital admissions (follow up: 28 days; assessed with: serious adverse events), better indicated by lower score												

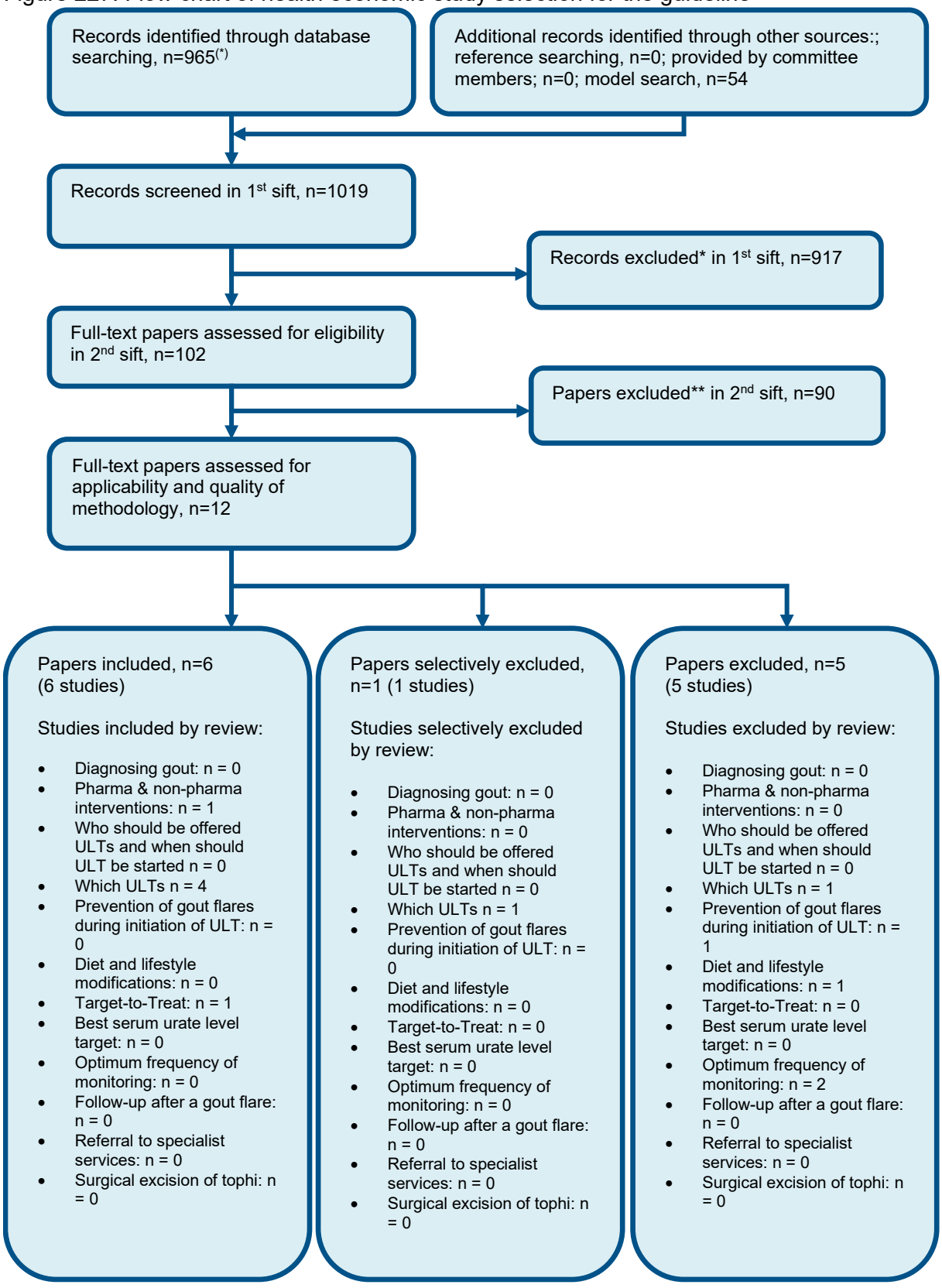
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cherry extract	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/40 (5.0%)	0/10 (0.0%)	**Peto OR 3.58 (0.11 to 118.71)**	**50 fewer (90 fewer to 190 more)**	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed 2 MIDsGRADE default MIDs were used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes... For continuous outcomes the MID was calculated as 0.4 for serum urate and 0.25 for number of gout flares.

Appendix G – Economic evidence study selection

Figure 227: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original economic modelling was undertaken for this review question.

Appendix J – Excluded studies

Clinical studies

Table 21: Studies excluded from the clinical review

Study	Exclusion reason
Al-Jarallah 1992[1]	Incorrect study design - literature review/overview
Bray 2013[4]	Systematic review - references checked
Chen 2019[6]	Systematic review - references checked
Choi 2005[7]	Incorrect study design - literature review/overview
Downey 2017[11]	Incorrect population - patients with hypertension (DASH trial)
Fanning 2018[13]	Systematic review - references checked
Jee 2018[15]	Systematic review - references checked
Juraschek 2016[16]	Incorrect population - overweight or obese adults without cardiovascular disease, gout status was not ascertained at baseline
Kelley 2011[18]	Systematic review references checked
Lee 2018[19]	Incorrect study design - cohort study, mendelian randomisation study between smoking behaviour and gout using single-nucleotide polymorphisms of smoking behaviour were selected as instrumental variables
Li 2011[20]	Incorrect study design - literature review/overview
Lin 2016[21]	Incorrect comparison/analysis - study assessed inhibitory kinetics and mechanism of dietary mechanism of vitamins D3 and B2 on Xantine oxidase
Milovanova 2017[22]	Not in English
Moi 2013[23]	Protocol for Cochrane review
Moi 2014[24]	Systematic review-references checked
Neogi 2014[26]	Incorrect study design - case-crossover study
Nielsen 2017[27]	Systematic review references checked
Park 2016[28]	Systematic review references checked
Porcelli 1994[29]	Incorrect study design - case-control study
Rho 2011[30]	Incorrect study design - literature review/overview
Vedder 2019[36]	Systematic review - references checked
Wang 2012[37]	Systematic review - references checked
Wang 2013[38]	Systematic review - references checked
Yang 2020[39]	Systematic review
Ying 2005[40]	Not in English
Zeng 2012[41]	Not in English

Zhang 2006[44]	Incorrect study design - case-crossover study
Zhang 2012[43]	Incorrect study design - case-crossover study
Zhang 2019[42]	Incorrect study design - case-crossover study

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 22: Studies excluded from the health economic review

Reference	Reason for exclusion
Chan 2014[5]	Excluded as rated not applicable. Differences in costs (from a New Zealand health care perspective) and outcomes were presented for Complementary and Alternative Medicines (CAM) users and non-CAM users however a detailed breakdown of costs was not provided. The study did not explicitly state what costs were borne by patients and what costs were paid by the health payer. No references for costs were provided.

1. al-Jarallah KF, Shehab DK, Buchanan WW. Rheumatic complications of alcohol abuse. Seminars in Arthritis and Rheumatism. 1992; 22(3):162-171

2. Andrés M, Sivera F, Falzon L, Buchbinder R, Carmona L. Dietary supplements for chronic gout. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010156. DOI: 10.1002/14651858.CD010156.pub2. http://dx.doi.org/10.1002/14651858.CD010156.pub2

3. Beecham J, Curtis L. Unit costs of health and social care 2020. Canterbury. Personal Social Services Research Unit University of Kent, 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/

4. Bray GA. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Advances in Nutrition. 2013; 4(2):220-225

5. Chan E, House ME, Petrie KJ, Horne A, Taylor WJ, Dalbeth N. Complementary and alternative medicine use in patients with gout: A longitudinal observational study. Journal of Clinical Rheumatology. 2014; 20(1):16-20

6. Chen PE, Liu CY, Chien WH, Chien CW, Tung TH. Effectiveness of cherries in reducing uric acid and gout: A systematic review. Evidence-Based Complementary & Alternative Medicine: eCAM. 2019:9896757

7. Choi HK. Dietary risk factors for rheumatic diseases. Current Opinion in Rheumatology. 2005; 17(2):141-146

8. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Archives of Internal Medicine. 2005; 165(7):742-748

9. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet. 2004; 363(9417):1277-1281

10. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. Annals of the Rheumatic Diseases. 2012; 71(6):929-934

11. Downey C. Should the DASH diet be recommended for gout patients? Journal of Clinical Outcomes Management. 2017; 24(1):9-11

12. Evans PL, Prior JA, Belcher J, Mallen CD, Hay CA, Roddy E. Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. Arthritis Research & Therapy. 2018; 20(1):136

13. Fanning N, Merriman TR, Dalbeth N, Stamp LK. An association of smoking with serum urate and gout: A health paradox. Seminars in Arthritis and Rheumatism. 2018; 47(6):825-842

14. Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. Internal Medicine Journal. 2015; 45(2):189-194

15. Jee Y, Jeon C, Sull JW, Go E, Cho SK. Association between smoking and gout: a meta-analysis. Clinical Rheumatology. 2018; 37(7):1895-1902

16. Juraschek SP, McAdams-Demarco M, Gelber AC, Sacks FM, Appel LJ, White KJ et al. Effects of lowering glycemic index of dietary carbohydrate on plasma uric acid levels: The omnicarb randomized clinical trial. Arthritis & Rheumatology. 2016; 68(5):1281-1289

17. Juraschek SP, Miller ER, Wu B, White K, Charleston J, Gelber AC et al. A randomized pilot study of dash patterned groceries on serum urate in individuals with Gout. Nutrients. 2021; 13(2):538

18. Kelley GA, Kelley KS, Hootman JM, Jones DL. Effects of community-deliverable exercise on pain and physical function in adults with arthritis and other rheumatic diseases: a meta-analysis. Arthritis Care and Research. 2011; 63(1):79-93

19. Lee YH. Assessing the causal association between smoking behavior and risk of gout using a Mendelian randomization study. Clinical Rheumatology. 2018; 37(11):3099-3105

20. Li S, Micheletti R. Role of diet in rheumatic disease. Rheumatic Diseases Clinics of North America. 2011; 37(1):119-133

21. Lin S, Zhang G, Liao Y, Gong D. The inhibitory kinetics and mechanism of dietary vitamins D3 and B2 on xanthine oxidase. Food & function. 2016; 7(6):2849-2861

22. Milovanova SY, Milovanov YS, Taranova MV, Dobrosmyslov IA. Effects of keto/amino acids and a low-protein diet on the nutritional status of patients with Stages 3B-4 chronic kidney disease. Terapevticheskii Arkhiv. 2017; 89(6):30-33

23. Moi J, Sriranganathan M, Edwards C, Buchbinder R. Lifestyle interventions for acute gout. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD010519. DOI: 10.1002/14651858.CD010519.pub2. http://dx.doi.org/10.1002/14651858.CD010519.pub2

24. Moi JH, Sriranganathan MK, Falzon L, Edwards CJ, van der Heijde DM, Buchbinder R. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. Journal of Rheumatology - Supplement. 2014; 92:26-32

25. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

26. Neogi T, Chen C, Niu J, Chaisson C, Hunter DJ, Zhang Y. Alcohol quantity and type on risk of recurrent gout attacks: An internet-based case-crossover study. American Journal of Medicine. 2014; 127(4):311-318

27. Nielsen SM, Bartels EM, Henriksen M, Waehrens EE, Gudbergsen H, Bliddal H et al. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Annals of the Rheumatic Diseases. 2017; 76(11):1870-1882

28. Park KY, Kim HJ, Ahn HS, Kim SH, Park EJ, Yim SY et al. Effects of coffee consumption on serum uric acid: systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2016; 45(5):580-586

29. Porcelli B, Vannoni D, Leoncini R, Pizzichini M, Pagani R, Marinello E. Free oxypurines in plasma and urine of gout patients before and after a purine-free diet. Advances in Experimental Medicine and Biology. 1994; 370:47-52

30. Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. Seminars in Nephrology. 2011; 31(5):410-419

31. Schlesinger N, Rabinowitz R, Schlesinger M. Pilot studies of cherry juice concentrate for gout flare prophylaxis. J Arthritis. 2012; 1(1):1-5

32. Singh JA, Green C, Morgan S, Willig AL, Darnell B, Saag KG et al. A randomized internet-based pilot feasibility and planning study of cherry extract and diet modification in gout. Journal of Clinical Rheumatology. 2020; 22:147-156

33. Singh JA, Willig AL, Darnell B, Green C, Morgan S, Weiss R et al. Patient-Centered Outcomes and Key Study Procedure Finalization in the Pilot Feasibility Gout Randomized Trial: Comparative Feasibility Study in GOUt, CHerry Extract Versus Diet Modification (Mini-GOUCH). JCR: Journal of Clinical Rheumatology. 2020; 26(5):181-191

34. Stamp LK, Chapman P, Frampton C, Duffull SB, Drake J, Zhang Y et al. Lack of effect of tart cherry concentrate dose on serum urate in people with gout. Rheumatology. 2020; 59(9):2374-2380

35. Stamp LK, O'Donnell JL, Frampton C, Drake JM, Zhang M, Chapman PT. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. Arthritis and Rheumatism. 2013; 65(6):1636-1642

36. Vedder D, Walrabenstein W, Heslinga M, de Vries R, Nurmohamed M, van Schaardenburg D et al. Dietary interventions for Gout and effect on cardiovascular risk factors: A systematic review. Nutrients. 2019; 11(12):04

37. Wang DD, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Cozma AI et al. The effects of fructose intake on serum uric acid vary among controlled dietary trials. Journal of Nutrition. 2012; 142(5):916-923

38. Wang M, Jiang X, Wu W, Zhang D. A meta-analysis of alcohol consumption and the risk of gout. Clinical Rheumatology. 2013; 32(11):1641-1648

39. Yang J, Li G, Xiong D, Chon TY, Bauer BA. The impact of natural product dietary supplements on patients with gout: A systematic review and meta-analysis of randomized controlled trials. Evidence-Based Complementary & Alternative Medicine: eCAM. 2020:7976130

40. Ying ZH, Ding ZH. Clinical rsearch on the rheumatism 2nd decoction in preventing primary gout recurrent. Zhejiang journal of Integrated Traditional Chinese and Western Medicine. 2005; 15(6):336-337

41. Zeng YC, Huang SF, Mu GP, Wang TF. Effects of adjusted proportional macronutrient intake on serum uric acid, blood lipids, renal function, and outcome of patients with gout and overweight. Chinese journal of clinical nutrition. 2012; 20(4):210-214

42. Zhang M, Zhang Y, Terkeltaub R, Chen C, Neogi T. Effect of dietary and supplemental omega-3 polyunsaturated fatty acids on risk of recurrent gout flares. Arthritis and Rheumatology. 2019; 71(9):1580-1586

43. Zhang Y, Chen C, Choi H, Chaisson C, Hunter D, Niu J et al. Purine-rich foods intake and recurrent gout attacks. Annals of the Rheumatic Diseases. 2012; 71(9):1448-1453

44. Zhang Y, Woods R, Chaisson CE, Neogi T, Niu J, McAlindon TE et al. Alcohol consumption as a trigger of recurrent gout attacks. American Journal of Medicine. 2006; 119(9):800.e813-800.e818