

Lifestyle Interventions for the Treatment of Gout: A Summary of 2 Cochrane Systematic Reviews

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ABSTRACT. Objective. To determine the efficacy and safety of lifestyle interventions for treating gout.

Methods. Two Cochrane systematic reviews assessed the efficacy and safety of lifestyle interventions for the treatment of acute and chronic gout. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials up to September 2011, and the 2010–2011 American College of Rheumatology and European League Against Rheumatism conference abstracts. Primary outcomes of interest were joint pain for acute gout, frequency of gout attacks for chronic gout, and withdrawals due to adverse events for both reviews.

Results. One trial met inclusion criteria for each review. An unblinded trial (19 participants), at high risk of bias, found that topical ice added to prednisolone and colchicine for acute gout resulted in significantly greater pain reduction at 1 week [mean difference (MD) –3.33 cm, 95% confidence interval (95% CI) –5.84 to –0.82 on 10 cm visual analog scale]. Adverse events were not described. The second trial (120 participants), at moderate risk of bias, compared enriched skim milk powder (glycomacropeptide and G600 milk fat extract) to non-enriched skim milk and lactose powders for treating chronic gout. There were no between-group differences in gout attack frequency over 3 months [MD –0.21 (95% CI –0.76 to 0.34)] or withdrawals due to adverse events [relative risk 1.27 (95% CI 0.53 to 3.03)].

Conclusion. While there is observational evidence for an association between lifestyle risk factors and gout development, there are no high quality trials to support or refute the use of lifestyle interventions for treating acute or chronic gout. (J Rheumatol Suppl. 2014 Sept; 92:26–32; doi:10.3899/jrheum.140459)

Key Indexing Terms:

GOUT

LIFESTYLE

DAIRY

DIET

ATTACKS

EFFICACY

Gout is a potentially progressive and debilitating form of chronic inflammatory arthritis, caused by deposition of monosodium urate crystals in synovial fluid and other tissues¹. Lifestyle risk factors associated with the development of gout include increased dietary intake of purine-rich foods (particularly meat and seafood), ethanol

(particularly beer and spirits), and fructose-sweetened drinks^{1,2,3,4}. For this reason, lifestyle modifications are commonly recommended in combination with urate-lowering medications (xanthine oxidase inhibitors, uricosuric agents, uricase agents) to help maintain monosodium urate levels below the serum saturation

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Based on 2 Cochrane Reviews published in the Cochrane Database of Systematic Reviews (CDSR) 2013, Issue 5, CD010039, and 2013, Issue

11, CD010519 (see www.thecochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

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point ($\leq 0.36 \mu\text{mol/l}$ or 6 mg/dl) to prevent crystal formation^{1,5}.

Although lifestyle interventions are commonly used in the management of chronic gout, the evidence for their benefits and safety in clinical trials has not been examined in a systematic review. The role of lifestyle interventions as an adjunct to medications for treating acute gout attacks is less well established, with theoretical concerns that applying lifestyle interventions that affect urate-lowering during the acute setting may cause harm. Therefore, a systematic review of the evidence from clinical trials for the safety and efficacy of lifestyle interventions for treating acute gout attacks (which has not previously been undertaken) is also warranted. The results of this review are likely to be important for informing clinical practice and/or determining whether further research is required to establish the value of lifestyle interventions for gout. This article is an abridged version of 2 Cochrane reviews that focused on lifestyle interventions for the treatment of acute⁶ and chronic gout⁷.

This article was developed as part of the 3e (Evidence, Expertise, Exchange) Initiative on the Diagnosis and Management of Gout. The objective of the current work was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was, "Which lifestyle changes (such as diet, alcohol intake, weight loss, smoking and/or exercise) are efficacious in the treatment/prevention of gout?"

MATERIALS AND METHODS

The reviews were carried out in accord with the guidelines outlined by the Cochrane Collaboration for systematic literature reviews⁸, and protocols for both reviews have been published^{9,10}.

Rephrasing the research question. The clinical question posed by the expert clinicians was rephrased to enable epidemiological enquiry using the PICO (Patient, Intervention, Comparator, Outcome) method¹¹. Patients were defined as adults diagnosed with gout [as per the author's description or according to the 1977 American College of Rheumatology (ACR) criteria for gout¹² or other criteria specified in the study]. The intervention was defined as one or more lifestyle interventions, such as weight loss, smoking cessation, exercise, increased coffee or dairy intake, and dietary modification (either elimination or reduced intake) of fructose-sweetened drinks, ethanol (particularly beer and spirits) and purine-rich foods (particularly meat and seafood). Comparators included placebo, urate-lowering medications (uricases, uricosuric agents, xanthine oxidase inhibitors) or other nonpharmacological interventions including lifestyle interventions used in treating gout. We included outcome measures that have been proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) network for use in clinical trials of acute and chronic gout¹³. The primary outcomes of interest were reduction of joint pain in acute gout studies, gout attack frequency in chronic gout studies, and participant withdrawals due to adverse events (AE) in both acute and chronic gout trials. The literature search was limited to randomized or quasirandomized controlled trials [RCT or controlled clinical trials (CCT)]. The secondary outcomes were reduction in target joint pain, serum urate normalization, activity limitation/function, health related quality of life, number and types of AE and serious adverse events (SAE), and patient global assessment.

Systematic literature search. We initially searched MEDLINE, EMBASE,

and the Cochrane Central Register of Controlled Trials (CENTRAL) for articles published between 1948 and September 29, 2011. The search strategy^{14,15} was developed in collaboration with an experienced librarian (see also online Appendix, available from www.3egout.com). We also searched the 2010–2011 conference abstracts from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) scientific meetings. The reference lists of included articles and relevant reviews were hand-searched to identify additional studies not retrieved by the aforementioned search strategy. Both searches were updated prior to publication of the 2 Cochrane reviews^{6,7} on April 5, 2013.

Selection of articles. Two review authors (JM, MS) independently screened all trials by title and abstract for eligibility for inclusion, and all relevant studies were retrieved for full-text review. Disagreements about study inclusion or exclusion were resolved by consensus or by discussion with a third author (RB) if needed.

Data extraction and quality appraisal. Data extraction was performed using standardized forms to collect information about study design, population characteristics, interventions, and outcomes, including adverse events. If required, authors were contacted to provide unpublished data. The risk of bias for included studies was assessed using the Cochrane risk of bias assessment tool, which included random sequence generation, allocation concealment, blinding of participants, study personnel and outcome assessor for each outcome measure, incomplete outcome data, and other sources of bias¹⁶. The risk of bias of each study was rated as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (either lack of information or uncertainty over the potential for bias).

Data analysis. For continuous data, results were analyzed as mean differences (MD) between the intervention and comparator group with 95% confidence intervals (95% CI). For dichotomous data, a relative risk (RR) with corresponding 95% CI was calculated. In cases of missing data, we assumed the missing values to have a poor outcome. Summarizing the data in a metaanalysis using a random effects model was planned if the included studies were sufficiently homogeneous that it was clinically meaningful to combine them¹⁷. Analysis was performed using Review Manager 5.2¹⁸.

RESULTS

Acute Gout

Search results. The original search yielded 695 references (Figure 1). After excluding 102 duplicate references, 247 references that were not RCT or CCT, 305 non-gout related references, and 40 with no or incorrect interventions, 1 article was retrieved¹⁹. This trial was published in Mandarin and was awaiting translation and classification at the time of review publication. One additional relevant trial was identified by hand search²⁰.

The updated search conducted for the Cochrane review on "lifestyle interventions for acute gout" yielded an additional 112 references¹⁴ (Figure 2). However, none of these fulfilled our inclusion criteria. We excluded 12 studies that were duplicates, 60 references that were unrelated to gout, 30 articles that were not RCT or CCT, and 10 with no or incorrect interventions.

Excluded studies. No studies were excluded after reviewing the full text of potentially eligible articles.

Included studies. The characteristics of the included trial²⁰ is summarized in Table 1. This study was a parallel group design RCT of 1 week duration, which included 19 participants and compared the addition of adjunctive topical ice therapy (applied for 30 min, 4 times/day) to the combination

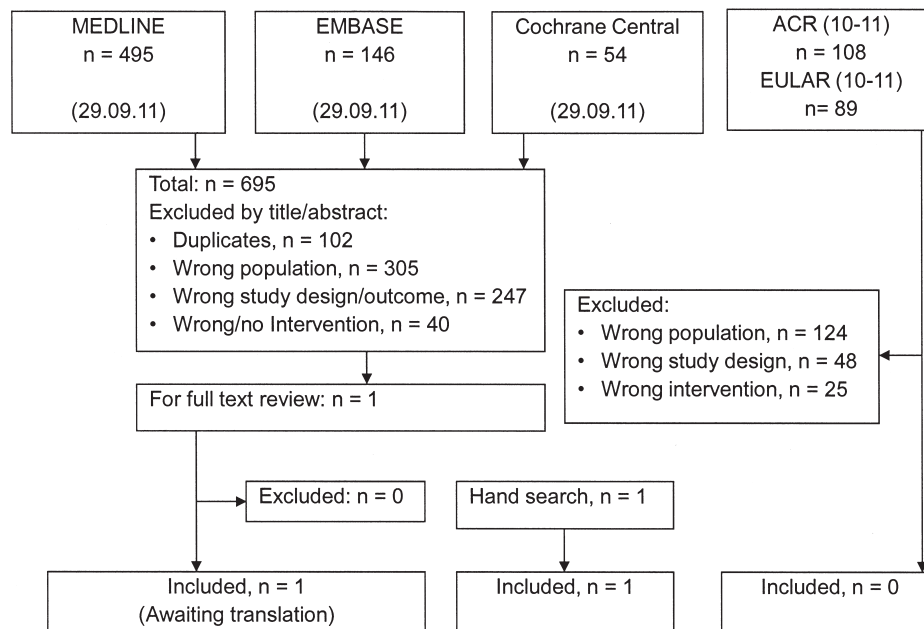


Figure 1. Literature search for acute gout, September 29, 2011, from which 2 articles were selected for detailed review. Two studies met inclusion criteria.

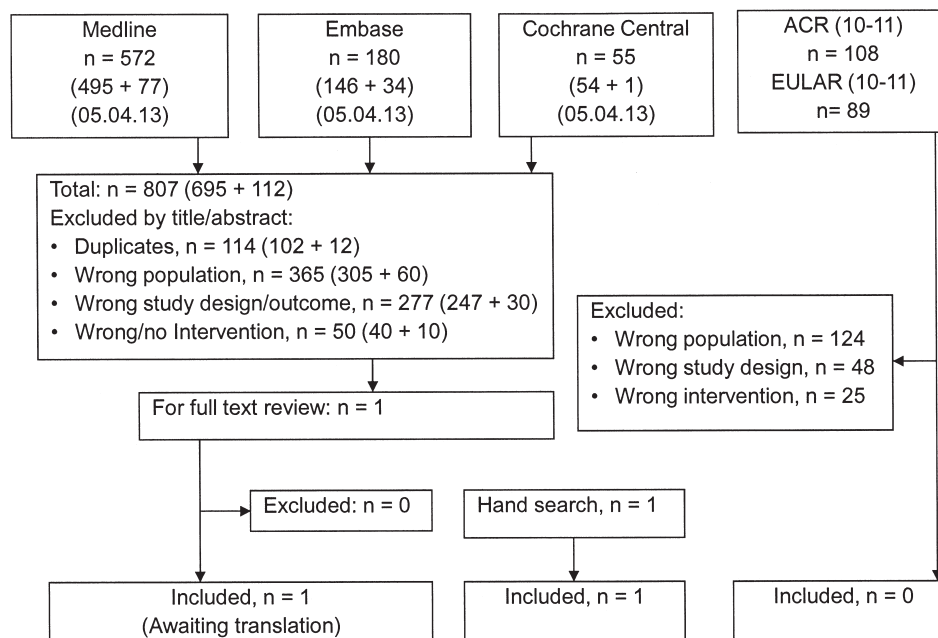


Figure 2. Literature search for Cochrane reviews on lifestyle interventions for acute gout, updated April 5, 2013. Two studies met inclusion criteria.

of oral prednisolone (30 mg/day) and colchicine (0.6 mg/day), against an identical medication regimen without topical ice for acute gout treatment. Stable background allopurinol therapy was continued throughout the trial. Study participant characteristics were not described. The

main outcome measures were reduction in joint pain [measured on 10 cm visual analog scale (VAS)] and joint swelling (joint circumference measured with a tape measure expressed in cm).

Risk of bias assessment. The results of the risk of bias

Table 1. Acute gout. Characteristics of the included study for the acute gout review.

Study	Population	Intervention	Comparator(s)	Outcome(s)	Study Design
Schlesinger 2002 ²⁰	19 participants with acute gout	Topical ice (30 min, 4 ×/day) & PNL 30 mg/day & colchicine 0.6 mg/day	PNL 30 mg/day & colchicine 0.6 mg/day	1. Pain, 2. Joint swelling, 3. SUA, 4. ESR, 5. Synovial fluid	RCT, non-blinded, 1 week

ESR: erythrocyte sedimentation rate; PNL: prednisolone; RCT: randomized controlled trial; SUA: serum uric acid.

assessment are presented in Table 2. The included trial was assessed to be at high risk of bias.

Efficacy. This trial showed that pain from an attack of acute gouty arthritis was significantly improved from baseline, when topical ice therapy was added as an adjunct to standard treatments (prednisolone, colchicine) [mean difference (MD) −3.33 cm, 95% CI −5.84 to −0.82]. There were no between-group differences in mean reduction of joint swelling (MD 2.07, 95% CI −1.56 to 5.70).

Safety. No AE or SAE were reported.

Chronic Gout

Search results. The original search yielded 695 references (Figure 3). After excluding 102 duplicate references, 247 references that were not RCT or CCT, 305 non-gout related references, and 40 with no or incorrect interventions, 1 article was retrieved¹⁹. The included trial was published in Mandarin and was awaiting translation and classification at the time of review publication. One additional trial was identified from searching the 2011 ACR abstracts. The identified abstract was subsequently published in full text and was included in this review²¹.

The updated search conducted for the Cochrane review on “lifestyle interventions for chronic gout” yielded a further 112 references¹⁵ (Figure 4). From the updated search, one additional trial published in Mandarin was identified²². This trial currently awaits translation and classification. We excluded the remaining references for the following reasons: 12 were duplicate studies, 59 were unrelated to gout, 30 were not RCT or CCT, and 10 had no or incorrect interventions.

Table 2. Acute gout. Risk of bias summary: Review of authors' judgments about each risk of bias item.

	Schlesinger 2002 ²⁰
Random sequence generation?	✓
Allocation concealment?	✗
Blinding of participants and personnel?	✗
Blinding of outcome assessment?	✗
Incomplete outcome data?	✓
Selective reporting?	?
Other sources of bias?	?

✗ High risk of bias; ✓ Low risk of bias; ? Unclear risk of bias.

Excluded studies. No studies were excluded following full-text review of potentially eligible articles.

Included studies. The characteristics of the included trial²¹ are summarized in Table 3. This 3-month RCT comprising 120 participants compared 2 control dairy products [lactose powder 15 g/day and skim milk powder (SMP) 15 g/day] to SMP enriched with dairy fractions glycomacropeptide (GMP) 1.5 g/day and 0.525 g/day of G600 milk fat extract (SMP/GMP/G600) for chronic gout treatment²¹. Participants were predominantly middle-aged white men who experienced frequent gout flares (at least 2 flares in the preceding 4 mos; as defined according to the EULAR/ACR gout flare definition²³) and had normal renal function. Stable background allopurinol therapy was continued in 55% of participants in each of the 3 study arms. The primary outcome was change in the frequency of gout flares. Secondary endpoints were changes in swollen (SJC, /66) and tender joint counts (TJC, /68), joint pain, Health Assessment Questionnaire (HAQ-II), patient global assessment of gout severity, C-reactive protein (CRP), serum urate concentration (SUA), and fractional excretion of uric acid.

Risk of bias assessment. Results of the risk of bias assessment are presented in Table 4. This trial was assessed to be at moderate risk of bias.

Efficacy. This trial demonstrated that all 3 dairy preparations, SMP enriched with GMP and G600, standard SMP, and lactose powder, significantly reduced the frequency of gout flares over a 3-month study period. After combining the 2 control groups (standard SMP, lactose powder) and calculating the standard deviation from the 95% CI, we found no statistical difference between SMP/GMP/G600 compared to the 2 control groups in terms of the change in the number of gout flares from baseline: mean difference (MD) −0.21 (95% CI −0.76 to 0.34).

The secondary outcomes for which we found a statistical difference between SMP/GMP/G600 and the 2 control groups include change in pain from self-reported gout flares (MD −1.03, 95% CI −1.96 to −0.10) and reduction in tender joint count from baseline (MD −0.49, 95% CI −0.85 to −0.12). A change of 1 point on a 10-point Likert scale may be a clinically meaningful result, given that Khanna, *et al* previously reported this to be the minimally clinically important difference (MCID) for pain reduction in their

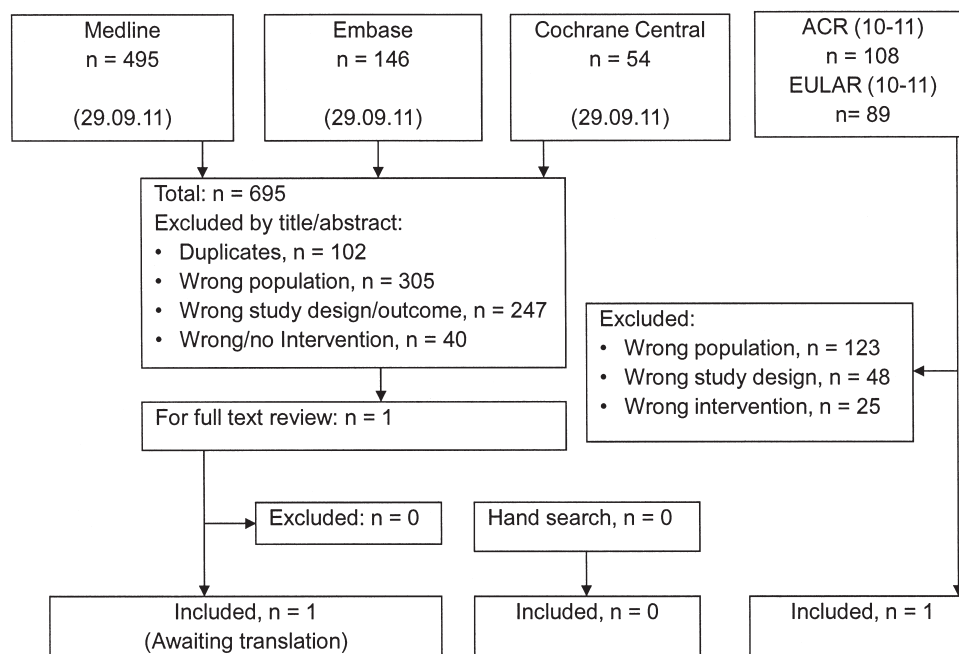


Figure 3. Literature search for chronic gout review September 29, 2011, from which 2 articles were selected for detailed review. Two studies met inclusion criteria.

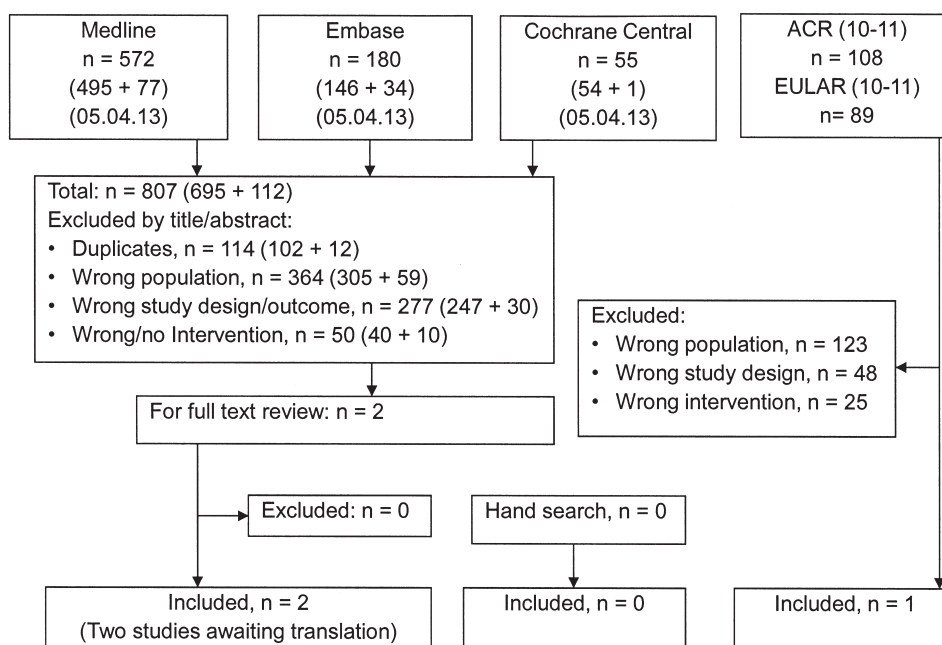


Figure 4. Literature search for the Cochrane review on lifestyle interventions for chronic gout, updated April 5, 2013. Three studies met inclusion criteria (1 additional trial retrieved).

RCT of rilonacept for preventing gout flares during initiation of allopurinol therapy²⁴. The clinical significance of a reduction in tender joint count by one-half of a joint over a 3-month period is less clear; although it might possibly benefit patients who experience recurrent monoarticular (in contrast to polyarticular) attacks of gout. No statistical

differences between groups were detected for change in SJC from baseline (MD -0.23, 95% CI -0.61 to 0.16), reduction in the number of self-reported flares (MD -0.49, 95% CI -1.08 to 0.09), improvement in physical function (MD -0.03, 95% CI -0.14 to 0.08), serum creatinine, serum urate concentration, and CRP.

Table 3. Chronic gout. Characteristics of the included study for the chronic gout review.

Study	Population	Intervention	Comparator(s)	Outcome(s)	Study Design
Dalbeth 2012 ²¹	120 participants with chronic gout; mean age 5th decade; gout duration 13–17 yrs; 20–43% with tophi, all normal renal function, SUA 0.41–44 mmol/l	SMP (GMP 1.5 g/day & G600 0.525 g/day)	Lactose powder 15 g/day & SMP 15 g/day	Primary: Gout flare frequency; secondary: 1. SJC, 2. TJC, 3. Pain, 4. PGA, 5. CRP, 6. SUA, 7. Fractional excretion UA, 8. HAQ-II, 9. AE	RCT, double blind, 12 weeks

AE: adverse events; CRP: C-reactive protein; GMP: glycomacropeptide; HAQ: health assessment questionnaire; PGA: patient global assessment; RCT: randomized controlled trial; SJC: swollen joint count; SMP: skim milk powder; SUA: serum uric acid; TJC: tender joint count; UA: uric acid.

Table 4. Chronic gout. Risk of bias summary: Review of authors' judgments about each risk of bias item.

	Dalbeth 2012 ²¹
Random sequence generation?	✓
Allocation concealment?	?
Blinding of participants and personnel?	✓
Blinding of outcome assessment?	?
Incomplete outcome data?	?
Selective reporting?	?
Other sources of bias?	?

✗: high risk of bias, ✓: low risk of bias, ?: unclear risk of bias

Safety. Study authors reported similar rates of AE and discontinuation between the 3 study groups. We found no differences between SMP/GMP/G600 compared to the 2 control groups in terms of withdrawals due to AE [7/40 SMP/GMP/G600 group versus 11/80 control groups; risk ratio (RR) 1.27, 95% CI 0.53 to 3.03], number of participants reporting AE (RR 0.97, 95% CI 0.66 to 1.45), and number of participants reporting serious adverse events (SAE) (2/40 SMP/GMP/G600 group versus 3/80 control groups; RR 1.33, 95% CI 0.23 to 7.66).

DISCUSSION

These are the first systematic reviews to summarize the evidence for the efficacy and safety of lifestyle interventions for treatment of patients with acute or chronic gout. The results served as an evidence base for 1 of the 10 recommendations regarding diagnosis and management of gout, which were generated by a multinational panel of rheumatologists as part of the 3e Initiative. A detailed description of the final recommendations can be found elsewhere²⁵.

There was low quality evidence, based on a single trial at moderate risk of bias, that ingestion of enriched SMP (GMP, G600), non-enriched SMP, and lactose powder were all associated with a small reduction in the frequency of gout flares (their primary measure of treatment benefit) over a 3-month study period, with no significant between-group differences. Small reductions in self-reported pain from gout

flares and a reduction in tender joint count from baseline were also reported, while no differences were seen in SJC, physical function, SUA, and CRP levels. There was no evidence of an increase in withdrawals due to AE or SAE in participants in the SMP/GMP/G600 group compared to controls, with gastrointestinal adverse effects cited as the most common complaint in both groups.

There was low quality evidence, from a single trial at high risk of bias, that there was a significant difference in pain reduction after 1 week (3.33 points greater improvement on a 10 cm VAS) when topical ice was used as an adjunct to combination treatment with oral prednisolone and colchicine. No significant between-group differences were identified in terms of improvement in joint swelling or synovial fluid variables (leukocyte count, volume) after 1 week. No AE or SAE were reported by the trial's authors.

There was a notable lack of trial data to support common lifestyle interventions used in both primary and secondary prevention of gout. Despite evidence from cross-sectional observational studies of a harmful association between the consumption of alcohol (beer, liquor), fructose, sugar-sweetened soft drinks, sweet fruits (apples, oranges), meat, seafood (oily fish, shellfish) and gout development, and the reported protective effects of decaffeinated coffee and vitamin C intake²⁶, there was no trial evidence to support these observations. While lifestyle and dietary modifications are likely to be beneficial in the management of comorbid cardiovascular disease and metabolic syndrome in patients with gout, their role in treating acute gouty arthritis or preventing gout flares in established disease remains unproven, due to the lack of evidence from high-quality trials.

Strengths of this review include the broad literature search used to identify relevant literature and to minimize the likelihood of missing relevant trials. We contacted the trial authors to obtain pertinent unpublished data and sought clarification of results, respectively, when there was incomplete or unclear reporting of trial data. Two authors undertook trial selection, data extraction, and "risk of bias" assessment independently to minimize bias.

A limitation of this review was that short-term trials may not be the optimal method for assessing the benefits and longterm sustainability of lifestyle modification for the treatment of people with chronic gout. This may require investigation with prospective longitudinal studies or registry data.

In conclusion, while there is good evidence from observational studies of an association between various lifestyle risk factors and the development of gout, there is a paucity of high-quality trial evidence to either support or refute the use of lifestyle interventions for treatment of acute or chronic gout. Further high-quality trials are required in this area.

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