# Table of Contents

- **Header** .................................................. 1
- **Abstract** .................................................. 1
- **Plain Language Summary** ................................. 2
- **Summary of Findings for the Main Comparison** .......... 4
- **Background** ............................................... 6
- **Objectives** ............................................... 7
- **Methods** ................................................. 7
- **Results** .................................................. 10
  - Figure 1 .................................................... 11
  - Figure 2 .................................................... 13
  - Figure 3 .................................................... 14
  - Figure 4 .................................................... 14
- **Discussion** ............................................... 14
- **Authors’ Conclusions** .................................... 15
- **Acknowledgements** ....................................... 16
- **References** .............................................. 18
- **Characteristics of Studies** ............................... 21
- **Data and Analyses** ...................................... 21
  - Analysis 1.1. Comparison 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment,
    Outcome 1 Ice vs. no Ice: mean pain reduction (10cm VAS) after one week ............................................ 21
  - Analysis 1.2. Comparison 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment,
    Outcome 2 Ice vs. No Ice: mean reduction in joint swelling (circumference in centimeters) after one week ........ 22
- **Appendices** ............................................... 22
- **Contributions of Authors** ............................... 31
- ** Declarations of Interest** .............................. 31
- **Sources of Support** ..................................... 31
Lifestyle interventions for acute gout

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ABSTRACT

Background

Although lifestyle interventions are often recommended in the management of chronic gout, the evidence from trial data of the benefits and safety of using lifestyle interventions for treating acute gout attacks have not previously been examined in a systematic review.

Objectives

The objective of this systematic review was to evaluate the benefits and safety of lifestyle interventions for the treatment of people with acute gout.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE for studies (up to 5 April 2013). We also searched the 2010 to 2011 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) abstracts and performed a handsearch of the reference lists of included articles.

Selection criteria

Studies were included if they were randomised or quasi-randomised controlled trials which compared lifestyle interventions to another therapy (active or placebo) in patients with acute gout. Outcomes of interest were the change in participant-reported pain in the target joint(s), target joint inflammation and function, health-related quality of life (HRQoL), patient global assessment, study participant withdrawals due to adverse events (AEs) and serious adverse events (SAEs).

Data collection and analysis

Two review authors independently applied methods recommended by The Cochrane Collaboration for the selection, appraisal, data collection and synthesis of studies. We assessed the quality of the body of evidence for each outcome using the GRADE approach.
Main results

Only one study (19 participants) at high risk of bias was included in the review. Patients were randomised to receive oral prednisolone and colchicine with or without concomitant topical ice therapy. Topical ice therapy provided significant additional benefit over oral prednisolone and colchicine alone with respect to pain, but did not significantly reduce swelling during acute gout episodes. Mean pain reduction with standard medical treatment was 4.4 cm on a 0 to 10 cm visual analogue scale (VAS) after one week; the addition of topical ice reduced pain by an additional 3.33 cm (95% CI 5.84 to 0.82), or an absolute reduction of 33% (8% to 58% reduction). Joint swelling was reduced by a mean of 3.8 cm in the standard medical treatment group; the addition of topical ice therapy did not reduce swelling significantly (mean difference (MD) 2.07 cm, 95% CI -1.56 to 5.70). Target joint function, HRQoL, patient global assessment, study participant withdrawals due to AEs and SEAs were not reported in this study.

Authors’ conclusions

There is low quality evidence, from a single trial at high risk of bias, that the addition of topical ice therapy to oral prednisolone and colchicine for oligoarticular attacks of acute gout results in significantly greater pain reduction at one week.

PLAIN LANGUAGE SUMMARY

Lifestyle interventions for treating acute gout attacks

This summary of a Cochrane review presents what we know from research about the effect of lifestyle modifications in the treatment of people with acute gout. There was one study included in this review, which looked at the benefits and safety of adding topical ice therapy to medications commonly used for treating acute gout (prednisolone and colchicine). Over a one week period, in addition to prednisolone and colchicine, ice was applied to the skin overlying the joints affected by acute gout, for half-an-hour, four times per day, to relieve symptoms of pain and warmth and to reduce signs of redness and swelling.

The review shows that in people with acute gout:

We are uncertain whether the reduction in pain seen with the addition of topical ice to standard treatment of prednisolone and colchicine, compared to prednisolone and colchicine alone, is a true effect because of the very low quality evidence.

Joint function, health-related quality of life, patient global assessment and side effects and complications were not reported.

We often do not have precise information about side effects and complications. Topical ice is likely to be a safe intervention.

What is gout and what are lifestyle interventions?

Gout is a very common cause of painful joint inflammation (arthritis) and is caused by urate crystals forming either within or around joints. The inflammation can lead to pain, redness, warmth and swelling of the affected joints, making the area difficult to touch or move. Some of the reasons why people get gout include their genetic make-up, being overweight, ingesting certain medications (for example cyclosporine), having impaired kidney function, and lifestyle habits such as drinking excessive amounts of alcohol and sugar-sweetened drinks.

Medications are the mainstay of acute gout treatment. Given the recognised association between certain lifestyle risk factors and gout development, lifestyle changes such as consuming more water, coffee, dairy milk and cherry juice, and having fewer sugar-sweetened drinks, alcoholic beverages, meat and seafood are commonly recommended to people with chronic gout to prevent recurrence of attacks.

Best estimate of what happens to people with acute gout using topical ice in addition to medications:

Joint pain (lower score means less pain)

People who used topical ice (for half-an-hour, four times per day for one week) in addition to medical treatment (oral prednisolone and colchicine) rated their pain 3.33 points lower on a 0 to 10 point pain scale (33% absolute improvement).

- People who used topical ice in addition to medical treatment (prednisolone and colchicine) rated their pain to be 2.25 points on a scale of 0 to 10.

- People who used medical treatment alone rated their pain to be 5.58 points on a scale of 0 to 10.

- Three people would need to be treated with topical ice for one person to benefit from pain relief.
Adverse events

Side effects or complications of using topical ice in addition to medical therapy were not reported in the study.
## Summary of Findings for the Main Comparison

**Lifestyle interventions for acute gout**

**Patient or population:** patients with acute gout  
**Settings:** hospital inpatient and outpatient clinic  
**Intervention:** lifestyle intervention

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Assumed risk</strong></td>
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<td><strong>Corresponding risk</strong></td>
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<td><strong>Control</strong></td>
<td>The mean pain reduction in the control group was 4.42 cm on a 10 cm visual analogue scale</td>
<td></td>
<td>19 (1 study)</td>
<td>⊕⊕⃝⃝ low¹,²</td>
<td>Absolute risk difference: 33% less pain with topical ice (95% CI -58% to -8%). Relative percentage change: -75% (95% CI -132% to -19%). NNT = 3</td>
</tr>
<tr>
<td><strong>Lifestyle intervention</strong></td>
<td>The mean pain reduction in the intervention group was 3.33 cm greater (5.84 to 0.82 greater)</td>
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<td><strong>Number of participant...</strong></td>
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<td><strong>withdrawals due to adverse...</strong></td>
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<tr>
<td><strong>Reduction of joint inflammation</strong></td>
<td>The mean reduction of joint inflammation in the control groups was 3.83 cm</td>
<td></td>
<td>19 (1 study)</td>
<td>⊕⊕⃝⃝ low¹,²</td>
<td>NNT not calculated, non-statistically significant³</td>
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<tr>
<td><strong>Joint function - not measured</strong></td>
<td>See comment</td>
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<td><strong>Health-related quality of life - not measured</strong></td>
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<td></td>
<td>Patient global assessment - not measured</td>
<td>See comment</td>
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<td>Not estimable</td>
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<td>Serious adverse events - not measured</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
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*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

---

1 Trial did not adequately conceal treatment allocation; blind study participants, personnel, outcome assessors
2 Small sample size
3 Number needed to treat to benefit (NNTB) not applicable when result is non-statistically significant. NNT for continuous outcomes calculated using the Wells calculator software available from the Cochrane Musculoskeletal Group editorial office
BACKGROUND

Description of the condition

Gout is a potentially progressive and debilitating form of chronic inflammatory arthritis that is caused by deposition of monosodium urate crystals in synovial fluid and other tissues (Neogi 2011). It affects 1% to 2% of adults in developed countries (Richette 2010) and can have a significant adverse impact upon a person’s quality of life. People who suffer from recurrent attacks frequently experience pain and disability, reduced health-related quality of life (HRQoL), reduced productivity and increased morbidity (Singh 2011a). Both its incidence and prevalence have appeared to rise in recent decades (Choi 2005a; Richette 2010). The reasons behind this are probably multi-factorial and potentially related to increasing longevity, rising rates of obesity and the metabolic syndrome, and shifts in dietary habits and lifestyle (Choi 2005a; Choi 2005b; Neogi 2011; Richette 2010). Hyperuricaemia, which is defined as a serum urate level ≥ 0.404 mmol/l or 6.8 mg/dL (the saturation point of urate in biological fluids based on in vitro studies), is the key predisposing factor for gout development (Neogi 2011; Schumacher 2008). Factors such as chronic hyperuricaemia, joint trauma or irritation (for example the first metatarsophalangeal joint is a site of mechanical stress), cooler body temperature (for example at the helix of the ear and the foot) and joint disease (for example osteoarthritis) all promote monosodium urate (MSU) crystal deposition within joints and tophus formation. The process of acute gout is thought to begin with the abrupt release of MSU crystals into the joint space, triggered by factors such as metabolic changes (for example increases or decreases in serum urate level) and mechanical trauma. Inside the joint cavity, MSU crystals are phagocytosed by synovial lining cells, which leads to the formation of a complex known as the inflammasome. The inflammasome releases a variety of pro-inflammatory cytokines (for example interleukin-1, tumour necrosis factor α, interleukin-8) and chemokines, resulting in neutrophil influx into the synovial tissue and fluid and generation of an intense urate-induced inflammatory reaction (Schumacher 2008). An alternate pathway by which extracellular MSU crystals can activate monocytes is via toll-like receptors (TLR), TLR2 and TLR4 (expressed by macrophages), which induce interleukin-1 transcription. In vivo studies support the crucial role of interleukin-1β (IL-1β) and its pathway in MSU-induced inflammation, highlighting IL-1β blockade as a key therapeutic target for future gout trials (Richette 2010). Acute gout attacks typically resolve over a period of seven to 10 days without intervention (Neogi 2011). However, treatment with pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs) (Janssens 2008a), colchicine (Schlesinger 2006b), and possibly glucocorticoids (Janssens 2008b; Wechalekar 2013) and adrenocorticotropic hormone (ACTH) (Axe 1988; Mikadashi 1994) may facilitate more rapid onset of pain relief and minimisation of disability. Resting the inflamed joint and applying topical ice may also help (Neogi 2011; Richette 2010). Lifestyle factors are another important contributing factor for the occurrence of acute gout attacks. Much of our current understanding of the lifestyle factors associated with gout is derived from large, cross-sectional, observational studies such as the Health Professionals Follow-up Study (HPFS) and the Third National Health and Nutrition Examination Survey (NHANES III) (Choi 2004c; Choi 2005b; Choi 2005c; Choi 2007b; Choi 2007c). The relationship between various lifestyle factors and gout can be summarised according to whether their association is regarded to increase the risk of, have no effect on, or decrease the risk of developing incident and recurrent gout. Lifestyle factors such as high dietary intake of purine-rich foods (particularly meat and seafood), ethanol (particularly beer and spirits), fructose-sweetened drinks and sweet fruits (apples, oranges), and weight gain and obesity are recognised risk factors for gout development (Choi 2004a; Choi 2004b; Choi 2010b; Neogi 2011; Singh 2011b). On the contrary, protein and purine-rich vegetable intake is regarded as having no effect on gout risk, having been vindicated as risk factors for gout, while ingestion of dairy products (low fat or skim milk), decaffeinated coffee, vitamin C and weight loss are considered to exert a protective effect against gout development (Choi 2010b; Neogi 2011; Richette 2010). For these reasons, lifestyle modifications are commonly recommended in combination with urate lowering medications for helping to reduce the risk of gout recurrence and chronic arthropathy developing in the long term (Neogi 2011; Richette 2010). However, the role of lifestyle interventions for treating acute gout attacks is less well established. Given that rapid reduction in serum urate levels is a recognised trigger for acute gouty arthritis (Richette 2012; Schumacher 2008), aggressive implementation of lifestyle interventions, such as those used in chronic gout treatment, may have an undesirable short-term effect of increasing the risk of gout flares. Therefore evaluation of the trial data, particularly in relation to the potential harm as well as benefits associated with using lifestyle interventions for treating acute gout attacks, is warranted.

Description of the intervention

Lifestyle interventions that may help in treating acute gout include resting the affected joint or joints and applying topical ice. Interventions employed in chronic gout for reducing gout attack frequency, such as maintaining adequate hydration, increasing coffee, dairy and cherry intake, and reducing dietary consumption of fructose-sweetened drinks, alcoholic beverages, meat and seafood (Richette 2010), will also be examined.

How the intervention might work
A mechanism by which reducing purine intake may help decrease acute gout attacks relates to free fatty acids (FFAs). The mere presence of monosodium urate (MSU) crystals in synovial fluid has been shown to be insufficient for triggering gout attacks and a 'second signal' appears to be necessary (Giamarellos-Bourboulis 2009; Joosten 2010; Richette 2012). A potential candidate is high levels of serum FFAs, which are increased following ingestion of purine-rich foods and alcohol. In the presence of FFAs, MSU crystals induce the production and release of IL-1β, a pro-inflammatory cytokine which is considered responsible for initiating clinical inflammation (Richette 2012). Therefore, reducing consumption of purine-rich foods and alcohol may facilitate the removal of the inciting agent required for initiating and sustaining acute gout attacks.

The ingestion of milk proteins (casein, lactalbumin, orotic acid) has been shown to exert a uricosuric effect in healthy people (Dalbeth 2010). Furthermore, in experimental models of acute gout, certain dairy fractions such as glycomacropeptide and G600 milk fat extract have been demonstrated to have anti-inflammatory effects (Dalbeth 2012), which may help with resolution of the acute inflammation seen with gout attacks. Cherry consumption has been demonstrated to have a urate lowering effect. Cherry products contain high levels of anthocyanins, which have anti-inflammatory properties that may help alleviate the pain and inflammation associated with gout attacks (Zhang 2012).

Adequate hydration is important for helping maintain the solubility of urate in joint fluid and avoiding intra-articular dehydration and subsequent increases in joint fluid urate concentration, supersaturation and crystal formation (Choi 2005a). The topical application of ice has been demonstrated to exert an analgesic effect in acutely inflamed joints (Schlesinger 2006a). In animal models of gouty arthritis, cooling joints has also been shown to reduce intra-articular temperatures, hyperaemia, cellular infiltration and crystal-induced inflammation and synovitis (Schlesinger 2006a).

Why it is important to do this review

Lifestyle interventions are commonly recommended in the management of chronic gout due to their urate lowering effects. However, the role of lifestyle interventions as an adjunct to medications for treating acute gout attacks is not well established. Indeed, there may be theoretical concerns that applying lifestyle interventions, which effect urate lowering, during the acute setting may cause harm. Therefore, a systematic review of the evidence from clinical trials on the safety and efficacy of lifestyle interventions for treating acute gout attacks (which has not previously been undertaken) is warranted. The results of the review are likely to be important for informing clinical practice and determining whether further research is required to establish the value of lifestyle interventions for acute gout.

**OBJECTIVES**

The objective of this systematic review was to evaluate the benefits and safety of lifestyle interventions for the treatment of people with acute gout.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All published randomised or quasi-randomised controlled trials which compared one or more lifestyle interventions to another therapy (active or placebo, pharmacological or non-pharmacological interventions) for treating acute gout were considered for inclusion. Only trials that were published as full articles or were available as a full trial report were included.

**Types of participants**

Adult patients (aged 18 years or older) diagnosed with acute gout, either via joint arthrocentesis with identification of uric acid crystals or according to the author's description. Populations that included a mix of people with acute gout and other musculoskeletal pain were excluded unless results for the acute gout population could be separated out from the analysis.

**Types of interventions**

All trials that evaluated one or a combination of lifestyle interventions for acute gout were eligible for inclusion. This included trials on smoking cessation, resting the affected joints, increasing intake of coffee, dairy milk or water, and reducing dietary intake of fructose-sweetened drinks, ethanol (particularly beer and spirits) and purine-rich foods (particularly meat and seafood). Trials that evaluated one or a combination of lifestyle interventions for chronic gout were excluded as these have been the subject of another Cochrane review (Moi 2013). Comparators could be:

1. placebo;
2. no treatment;
3. one lifestyle intervention versus another lifestyle intervention;
4. paracetamol;
5. non-steroidal anti-inflammatory drugs (NSAIDs);
6. colchicine;
7. glucocorticoids (intra-articular, systemic);
8. interleukin-1 (IL-1) inhibitors;
9. combination therapy (combinations of any of the above).
**Types of outcome measures**

We included the outcome measures for use in clinical trials of acute gout that have been proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) network (Grainger 2009).

**Main outcomes**

1. **Benefits**: participant-reported pain reduction in the target joint(s) affected by acute gout, e.g., 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.
2. **Safety**: number of study participant withdrawals due to adverse events (AEs).

**Other outcomes**

1. Reduction of joint inflammation (joint swelling, erythema, temperature), e.g., measured using a VAS or numerical rating scale
2. Function of the target joint
3. Health-related quality of life (HRQoL) as measured by generic instruments (such as the Medical Outcomes Study Short-Form-36 Survey (SF-36))
4. Patient global assessment, e.g., as measured on the Patient's Global Assessment of Response to Treatment (PGART)
5. Proportion of participants with serious adverse events (SAEs), defined as AEs that are fatal, life-threatening or require hospitalisation

For the purpose of this review, if feasible, we planned to group the outcomes into short-term (up to two weeks), medium-term (two to six weeks) and long-term (more than six weeks) outcomes.

**Searching other resources**

We searched the American College of Rheumatology (ACR) and EUropean League Against Rheumatism (EULAR) conference abstracts from 2010 and 2011. We handsearched the reference lists of included articles and relevant reviews to identify any additional studies not retrieved by the aforementioned search strategy.

**Data collection and analysis**

**Selection of studies**

Two review authors (JM, MS) independently assessed all retrieved trials to identify those that fulfilled the criteria for inclusion in this systematic review. We retrieved all relevant articles in full text for closer examination. Disagreement about study inclusion or exclusion was resolved by consensus or by discussion with a third author (RB) if needed. Studies were translated into English where necessary.

**Data extraction and management**

Two authors (JM, MS) independently extracted the following relevant information from included trials using a predefined data extraction form: study design, characteristics of the study population (age, gender, presence or absence of concurrent urate lowering medication use or tophi), lifestyle interventions, control interventions, outcome measures (mean and standard deviation for continuous outcomes, number of events and participants for dichotomous outcomes), timing of outcome assessment, and methodological domains relevant to 'Risk of bias' assessment. We resolved differences in data extraction by referring back to the original articles and establishing consensus. A third author (RB) was consulted to help resolve differences if necessary.

**Assessment of risk of bias in included studies**

We assessed the potential for bias in the included studies using the Cochrane Collaboration’s tool for assessing risk of bias (Higgins 2011). Two review authors (JM, MS) independently assessed the risk of bias in included trials and resolved any disagreements by consensus or consultation with a third author (RB) if necessary. We assessed the following methodological domains:

1. **random sequence generation**, to determine if the method of generating the randomisation sequence was adequate to prevent biased allocation to interventions;
2. **allocation concealment**, to determine if adequate methods were used to conceal allocation to interventions;
3. **blinding of participants, personnel and outcome assessors for each outcome measure**, to determine if adequate methods to prevent knowledge of the allocated interventions by study participants, personnel and outcome assessors occurred during the study;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other potential sources of bias.

To determine the risk of bias of an included study, for each criterion we evaluated the presence of sufficient information and the likelihood of potential bias. We rated each of these criteria either as 'low risk', 'high risk' or 'unclear risk' (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect

We planned to summarise the data in a meta-analysis only if there was sufficient clinical and statistical homogeneity. For continuous data, we analysed results as mean differences (MD) between the intervention and comparator groups, with corresponding 95% confidence intervals (CI). The MD between treated group and control group was weighted by the inverse of the variance in the pooled treatment estimate. However, when different scales were used to measure the same conceptual outcome (for example, function or pain), we calculated standardised mean differences (SMDs) instead, with corresponding 95% CIs. SMDs were calculated by dividing the MD by the standard deviation, resulting in a unitless measure of treatment effect. For dichotomous data, we calculated a risk ratio (RR) with corresponding 95% CI.

Unit of analysis issues

For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, we planned to include the same group of participants only once in the meta-analysis. In the event that cross-over trials were identified in which the reporting of continuous outcome data precluded paired analysis, these data were not included in a meta-analysis in order to avoid unit of analysis errors. Where carry-over effects were thought to exist, and where sufficient data existed, data from the first period only were included in the analysis (Higgins 2011). We planned to extract data from all time points and combine them into short-term (up to two weeks), medium-term (over two weeks to six weeks) and long-term (more than six weeks) outcomes, though this depended on the feasibility of doing so from the available data. If more than one time point was reported within the subgroup (for example, at one week and two week follow-up), we extracted the last outcome.

Dealing with missing data

Where data were missing or incomplete, we sought further information from the study authors. In cases where individuals were missing from the reported results and no further information was forthcoming from the study authors, we assumed the missing values to have a poor outcome.

For dichotomous outcomes that measured adverse events (for example, number of withdrawals due to adverse events) the withdrawal rate was calculated using the number of patients that received treatment as the denominator (worst-case analysis). For dichotomous outcomes that measure benefits (for example, patient-reported reduction in joint pain during acute gout) we calculated the worst-case analysis using the number of randomised participants as the denominator.

For continuous outcomes (for example, pain) we calculated the MD or SMD based on the number of patients analysed at the time point. If the number of patients analysed was not presented for each time point, we used the number of randomised patients in each group at baseline. Where possible, we computed missing standard deviations from other statistics such as standard errors, CIs or P values according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If standard deviations were not able to be calculated, we planned to impute them (for example, from other studies in the meta-analysis (Higgins 2011)).

Assessment of heterogeneity

Prior to meta-analysis, we planned to assess studies for clinical homogeneity with respect to type of therapy, control group and the outcomes. For any studies judged as clinically homogeneous, we planned to estimate statistical heterogeneity using the I² statistic (Deeks 2011), using the following as a rough guide for interpretation: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as I² ≥ 75%), we planned to explore the data further, including subgroup analysis, in an attempt to explain the heterogeneity.

Assessment of reporting biases

In order to determine whether reporting bias was present, we determined whether the protocol for the RCT was published before recruitment of patients to the study was started. For studies published after 1 July 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch/) (DeAngelis 2004). We evaluated whether selective reporting of outcomes was present (outcome reporting bias).

We compared the fixed-effect model estimate against the random-effects model to assess the possible presence of small sample bias in the published literature (that is, in which the intervention effect is more beneficial in smaller studies). In the presence of small sample bias, the random-effects model estimate of the intervention is more beneficial than the fixed-effect model estimate (Sterne 2011). We planned to further explore the potential for reporting bias using funnel plots, if more than 10 studies were included.
Data synthesis
Where studies were sufficiently homogeneous that it remained clinically meaningful for them to be pooled, we planned to perform meta-analysis using a random-effects model, regardless of the $I^2$ results. We planned to perform analyses using the Cochrane Collaboration’s statistical software, Review Manager 2011, and produce forest plots.

Subgroup analysis and investigation of heterogeneity
Where sufficient data were available, the following subgroup analysis was planned:
1. polyarticular versus monoarticular and oligoarticular gout attacks.

Sensitivity analysis
Where sufficient studies existed, sensitivity analyses were planned to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs) and inadequate blinding of study participants, personnel and outcome assessors.

Presentation of key results
We produced a ‘Summary of findings’ table to illustrate key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the most important patient-relevant outcomes as recommended by The Cochrane Collaboration (Schünemann 2011a). The ‘Summary of findings’ table included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Schünemann 2011b). In addition to the absolute and relative magnitude of effect provided in the ‘Summary of findings’ table, for dichotomous outcomes we calculated the number needed to treat to benefit (NNTB) or the number needed to treat to harm (NNTH) from the control group event rate (unless the population event rate was known) and the risk ratio using the ‘Visual Rx’ programme (Cates 2008). For continuous outcomes, we calculated the NNT using the Wells calculator software, available at the Cochrane Musculoskeletal Group editorial office (http://musculoskeletal.cochrane.org/). We determined the minimal clinically important difference (MCID) for each outcome for input into the calculator.

We presented the following outcomes (at the latest time point) in a ‘Summary of findings’ table (Schünemann 2011a; Schünemann 2011b):
1. participant-reported pain reduction in the target joint(s);
2. reduction of inflammation;
3. function of the target joint;
4. HRQoL;
5. patient global assessment;
6. number of study participant withdrawals due to AEs;
7. proportion of participants with SAEs.

RESULTS

Description of studies
Results of the search
The search strategy yielded 808 references (see Figure 1). After excluding 114 duplicate references, 277 references that were not RCTs or CCTs, 364 non-gout related references, and 50 references with no or incorrect interventions, we retrieved three articles for full assessment. Only one study published in English was found to meet our inclusion criteria (Schlesinger 2002). Two other trials were published in Mandarin and are awaiting translation and classification (Zeng 2012; Zhao 2009) (see Characteristics of studies awaiting classification). The review will be updated to include data from these studies if they are found to meet the inclusion criteria.
Figure 1. Study flow diagram.

807 records identified through database searching

1 additional record identified through other sources

694 records after duplicates removed

694 records screened:
Not gout-related, n=364
Not RCT or CCT, n=277
Wrong/no intervention, n=50

691 records excluded

3 full-text articles assessed for eligibility

0 full-text articles excluded

3 studies included in qualitative synthesis

0 studies included in quantitative synthesis (meta-analysis)
(reason: single trial included)
Included studies
Details of the included trial are provided in the table ‘Characteristics of included studies’. This RCT was performed in the USA, was of parallel group design, included 19 participants, and was of one week's duration (Schlesinger 2002).

Study participants
Schlesinger 2002 included participants with gout, proven through arthrocentesis and isolation of monosodium urate (MSU) crystals in the synovial fluid. Participants were recruited during the acute phase of a gouty arthritis attack and stable background allopurinol therapy was continued during the trial. No other demographic information on study participants was provided, despite contacting the trial author.

Interventions
Schlesinger 2002 compared the addition of topical ice therapy (applied for 30 minutes, four times per day) to the combination of oral prednisolone (30 mg/day x 2 days, 20 mg/day x 2 days, 10 mg/day x 2 days) and colchicine (0.6 mg/day) against an identical medication regimen without topical ice therapy, over six days.

Timing of follow-up
Schlesinger 2002 reported outcomes at a single time point, one week following topical ice intervention.

Outcome assessment
Schlesinger 2002 reported two of the five essential outcome domains proposed by the OMERACT network for use in studies of acute gout (Schumacher 2009). These study endpoints included a reduction in joint pain (measured using a 10 cm VAS) and swelling (recorded as the circumference of gout affected joints, using a tape measure, expressed in centimetres). Schlesinger 2002 also reported laboratory values for serum uric acid (SUA), erythrocyte sedimentation rate (ESR) and synovial fluid analysis (leukocyte count, fluid volume) pre- and post-intervention with topical ice. The number and types of AEs and SAEs were not reported.

Excluded studies
No studies were excluded after review of the full texts of potentially eligible articles.

Risk of bias in included studies
The results of the risk of bias assessment are presented in Figure 2. The included trial failed to meet all of the criteria for low risk of bias and the results may therefore be biased.
Allocation

Schlesinger 2002 adequately described their method of sequence generation but their method of allocation concealment (“folded paper note”) was assessed to be insufficient for blinding investigators to treatment allocation and was deemed high risk of bias.

Blinding

It was unclear whether Schlesinger 2002 blinded participants, personnel, or outcome assessors. Due to the nature of the intervention (topical ice therapy) it would be difficult to blind participants.

Incomplete outcome data

Schlesinger 2002 reported that there were no study participant withdrawals and provided the outcome data for all randomised participants.

Selective reporting

Schlesinger 2002 reported the data for all pre-specified efficacy outcomes.

Other potential sources of bias

No other potential sources of bias were identified.
Effects of interventions

See: Summary of findings for the main comparison Lifestyle interventions for acute gout
See: Summary of findings for the main comparison for the main comparison.

Topical ice therapy plus prednisolone and colchicine versus prednisolone and colchicine

Data from one unblinded trial of acute gout (19 participants) (Schlesinger 2002) showed that the pain from an attack of acute gouty arthritis was significantly improved from baseline when topical ice therapy was added as an adjunct to oral prednisolone tapered over six days (30 mg x 2 days, 20 mg x 2 days, 10 mg x 2 days) and colchicine 0.6 mg/day x 6 days) (MD -3.33 cm, 95% CI -5.84 to -0.82) (Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment. Outcome 1.1: ice versus no ice: mean pain reduction (10 cm VAS) after one week.

No statistical difference was identified in the results between the two groups when comparing mean reduction of joint swelling (MD 2.07 cm, 95% CI -1.56 to 5.70) (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment. Outcome 1.2: ice versus no ice: mean reduction in joint swelling (circumference in centimeters) after one week.

Other outcomes that were not included in this review but were reported in Schlesinger 2002 were the following. There were no between-group differences in synovial fluid analysis in terms of mean reductions in synovial fluid leukocyte count (MD 11/mm$^3$, 95% CI -9565 to 9707) or synovial fluid volume (MD 16.08 mL, 95% CI -6.45 to 38.61) (data not shown).

Discussion

Summary of main results

One unblinded trial of 19 participants, at high risk of bias, found that there was a significant difference in improvement in pain at one week (3.33 points greater improvement on a 10 cm VAS) when topical ice was used as an adjunct to a combination of oral prednisolone and colchicine. No significant between-group differences were identified in terms of improvement in joint swelling at one week. Information about AEs or SAEs were not reported.

Overall completeness and applicability of evidence

There was a notable lack of trial data to support commonly prescribed lifestyle interventions used in acute gout treatment.
Despite evidence from cross-sectional observational studies of a harmful association between the consumption of alcohol (beer, liquor), fructose-sweetened soft drinks, sweet fruits (apples, oranges), meat, seafood (oily fish, shellfish) and gout development (Choi 2010a; Choi 2010b), the reported protective effects of ingesting water, dairy milk, coffee, cherries, vitamin C for preventing gout recurrence (Choi 2004a; Choi 2005a; Choi 2007a; Dalbeth 2010; Zhang 2012), and the assumed analgesic benefits of resting inflamed joints during an acute attack of gouty arthritis, there was no trial evidence to support these observations.

Quality of the evidence

We judged the evidence on lifestyle interventions for acute gout treatment as low quality, according to the GRADE assessment, since it was based on a single small trial, which met the criteria for high or unclear risk of bias in five out of seven domains of bias assessment, including lack of blinding of participants and study assessors, and reporting bias. We suspect that the small number of trials identified is likely to be a reflection of a lack of high quality research in the area rather than publication bias.

Potential biases in the review process

We are confident that the broad literature search used in this review has captured relevant literature and minimised the likelihood that we missed any relevant trials. In the event of incomplete or unclear reporting of trial data, the trial authors were contacted by the review authors to obtain pertinent unpublished data or clarification of results was sought, respectively. In the case of eligible trials being published in languages other than English, translation of trials was requested. Trial selection, data extraction, and risk of bias assessment were undertaken independently by two authors to minimise bias.

Agreements and disagreements with other studies or reviews

The findings of our review are consistent with the conclusions of the recently updated 2012 American College of Rheumatology (ACR) guidelines for management of gout (Khanna 2012). In addition to recommendations to institute prompt pharmacological treatment for acute gout, providing instructions for managing recurrence, and providing patient education on lifestyle, dietary and other triggers of acute attacks, the authors also advocated topical ice application as an appropriate adjunctive measure to one or more pharmacologic therapies for acute gouty arthritis. In a separate cochrane review of lifestyle interventions for the treatment of chronic gout, a single trial, at moderate risk of bias, showed that skim milk enriched with the dairy fractions glycomacropeptide and G600 provided no additional benefit over standard skim milk or lactose powder in reducing the frequency of gout flares (Moi 2013).

Authors’ conclusions

Implications for practice

While there is good evidence from observational studies of an association between various lifestyle risk factors and development of gout, there is a paucity of high quality evidence to either support or refute the use of lifestyle interventions for treatment of acute gout. While based upon very low quality evidence, one week of topical ice may be a useful adjunct to medical treatment for managing oligoarticular attacks of acute gout, and is likely to be safe.

Implications for research

Randomised controlled trials assessing lifestyle interventions to treat acute gout are needed before any conclusions can be made about the role of lifestyle interventions for reducing the symptoms of acute gout.

Planned trials should consider inclusion of the proposed set of outcomes proposed by OMERACT for studies of acute gout, including reduction in target joint pain, swelling, tenderness, patient global assessment, physician global assessment and functional disability (Schumacher 2009). The CONSORT statement should also be used as a guide for both designing and reporting trials (Boutron 2008).

Trial reporting should include the methods of randomisation and treatment allocation concealment; blinding of study participants, study personnel and outcome assessment; follow-up of all participants who entered the trial; and complete reporting of outcomes. Sample sizes should be reported and have adequate power to answer the research question; ideally trials should assess both the benefits and risks of lifestyle interventions. To enable the comparison and pooling of the results of randomised controlled trials, we suggest that future trials report means with standard deviations for continuous measures or number of events and total numbers analysed for dichotomous measures, and use standardised measurement tools for reporting relevant outcomes.

Acknowledgements

The authors thank Louise Falzon, former Trials Search Co-ordinator of the Cochrane Musculoskeletal Group, for designing the search strategy.
References to studies included in this review

Schlesinger 2002  {published data only (unpublished sought but not used)}


References to studies awaiting assessment

Zeng 2012  {published data only}


Zhao 2009  {published data only}


Additional references

Axelrod 1988


Boutron 2008


Cates 2008

Dr Christopher Cates. Dr Chris Cates’ EBM website, Visual Rx. 3. Dr Christopher Cates, 2008.

Choi 2004a


Choi 2004b


Choi 2004c


Choi 2005a


Choi 2005b


Choi 2005c


Choi 2007a


Choi 2007b


Choi 2007c


Choi 2010a


Choi 2010b


Dalbeth 2010


Dalbeth 2012


DeAngelis 2004

Deeks 2011

Giamarellos-Bourboulis 2009

Grainger 2009

Higgins 2011

Janssens 2008a

Janssens 2008b

Joosten 2010

Khanna 2012

Mikadashi 1994

Moi 2013

Neogi 2011

Review Manager 2011

Richette 2010

Richette 2012

Schlesinger 2006a

Schlesinger 2006b

Schumacher 2008

Schumacher 2009

Schünemann 2011a

Schünemann 2011b

Singh 2011a
Singh JA, Taylor WJ, Simon LS, Khanna PP, Stamp LK, McQueen FM, et al. Patient-reported outcomes in...
## Characteristics of included studies [ordered by study ID]

### Schlesinger 2002

| Methods | Randomised controlled trial  
Duration: one week  
Withdrawals: nil  
Sample size calculation: not stated  
Intention-to-treat analysis: not performed |
| --- | --- |
| Participants | 19 participants  
Inclusion criteria:  
- not reported  
Exclusion criteria:  
- not reported |
| Interventions | Intervention 1: topical ice therapy + oral prednisone 30mg tapered over 6 days (30mg x 2 days, 20mg x 2 days, 10mg x 2 days) + colchicine 0.6 mg/day (n=10)  
Intervention 2: oral prednisone 30 mg tapered over 6 days (30mg x 2 days, 20mg x 2 days, 10mg x 2 days) + colchicine 0.6 mg/day (n=9) |
| Outcomes | Assessed at baseline and one week later:  
1. pain (VAS)  
2. circumference of the affected joint (cm)  
3. synovial fluid WBC count  
4. synovial fluid volume |
| Notes | We attempted to contact the trial author for information not reported in the trial (e.g., patient demographics, blinding, adverse events) |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</thead>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Patients were randomly assigned to one of 2 groups (by blindly drawing a folded paper note).”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Comment: method of folding of paper note used for allocation concealment could easily have been tampered with</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias)  
All outcomes | High risk | Comment: not described. Clarification was sought from the trial author but a reply was not received. Due to the nature of the intervention (ice) it is unlikely that participants could have been blinded |
### Schlesinger 2002  (Continued)

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<th>Bias Type</th>
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<tr>
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<td>Comment: not described. Clarification was sought from the trial author but a reply was not received. Due to the nature of the intervention (ice) it is unlikely that participants could have been blinded</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Comment: no study withdrawals, or excluded data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear</td>
<td>Comment: all pre-specified efficacy outcome data were reported. No adverse events described</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear</td>
<td>Comment: sources of funding not described, and trial not registered with clinical trials registry</td>
</tr>
</tbody>
</table>

### Characteristics of studies awaiting assessment  [ordered by study ID]

#### Zeng 2012

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<th>Details</th>
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</thead>
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<tr>
<td>Methods</td>
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<td>Participants</td>
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<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Notes</td>
<td>Awaiting translation</td>
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#### Zhao 2009

<table>
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<td>Interventions</td>
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<td>Outcomes</td>
<td></td>
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<tr>
<td>Notes</td>
<td>Awaiting translation</td>
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## DATA AND ANALYSES

Comparison 1. Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ice vs. no Ice: mean pain reduction (10cm VAS) after one week</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2 Ice vs. No Ice: mean reduction in joint swelling (circumference in centimeters) after one week</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment, Outcome 1 Ice vs. no Ice: mean pain reduction (10cm VAS) after one week.

Review: Lifestyle interventions for acute gout

Comparison: 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment

Outcome: 1 Ice vs. no Ice: mean pain reduction (10cm VAS) after one week

| Study or subgroup | Ice | | No ice | | Mean Difference | | Mean Difference |
|-------------------|-----||        | |               | |               |
| Schlesinger 2002  | 10  | | 9      | | -7.75 (2.58)   | | -4.42 (2.96)   |
|                   |     | |        | |                | | -3.33 [-5.84, -0.82] |
| Subtotal (95% CI) | 0   | | 0      | |                | | 0.0 [ 0.0, 0.0 ] |

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

---

Lifestyle interventions for acute gout (Review)

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Analysis 1.2. Comparison 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment, Outcome 2 Ice vs. No Ice: mean reduction in joint swelling (circumference in centimeters) after one week.

Review: Lifestyle interventions for acute gout

Comparison: 1 Medical treatment (prednisolone and colchicine) versus topical ice plus medical treatment

Outcome: 2 Ice vs. No Ice: mean reduction in joint swelling (circumference in centimeters) after one week

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ice</th>
<th>No ice</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlesinger 2002</td>
<td>10</td>
<td>9</td>
<td>-2.07 [ -5.70, 1.56 ]</td>
<td>-2.07 [ -5.70, 1.56 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Gout explode all trees
#2 gout*:ti,ab
#3 (#1 OR #2)
#4 MeSH descriptor Ethanol explode all trees
#5 ethanol:ti,ab
#6 MeSH descriptor Alcohol-Related Disorders explode all trees
#7 MeSH descriptor Alcohol Drinking, this term only
#8 alcohol*:ti,ab
#9 MeSH descriptor Exercise explode all trees
#10 MeSH descriptor Exercise Therapy explode all trees
#11 MeSH descriptor Exercise Movement Techniques explode all trees
#12 MeSH descriptor Physical Education and Training explode all trees
#13 MeSH descriptor Physical Fitness, this term only
#14 MeSH descriptor Physical Exertion, this term only
#15 MeSH descriptor Sports explode all trees
#16 exercis*:ti,ab
#17 sport*:ti,ab
#18 (physical* next (fit* or exert* or activ*)):ti,ab
#19 (run* or jog* or walk*):ti,ab
#20 (swim* or cycle* or bicycl*):ti,ab
#21 train*:ti,ab
#22 kinesi?therap*:ti,ab
#23 ((weight or muscle*) next (strength* or resistance)):ti,ab
#24 endurance:ti,ab
#25 MeSH descriptor Tobacco explode all trees
#26 MeSH descriptor Tobacco Use Disorder, this term only
#27 MeSH descriptor Tobacco Use Cessation explode all trees
#28 MeSH descriptor Tobacco Smoke Pollution explode all trees
#29 MeSH descriptor Nicotine, this term only
#30 smok*:ti,ab
#31 (cigarette* or cigar* or pipe*):ti,ab
#32 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)
#33 MeSH descriptor Weight Loss explode all trees
#34 weight loss:ti,ab
#35 (weight near/2 (lo* or reduc* or eliminat*)):ti,ab
#36 ((body mass index or bmi) near/3 (los* or reduc* or decreas* or low*)):ti,ab
#37 (Waist circumference near/2 (reduc* or low* or small*)):ti,ab
#38 (Waist size near/2 (reduc* or low* or small*)):ti,ab
#39 energy next restrict*:ti,ab
#40 calor* near/2 (reduc* or low* or small*):ti,ab
#41 MeSH descriptor Anti-Obesity Agents explode all trees
#42 (appetite near/2 suppress*):ti,ab
#43 orlistat:ti,ab
#44 xenical:ti,ab
#45 alli:ti,ab
#46 tetrahydrolipstatin:ti,ab
#47 phentermine:ti,ab
#48 phenyl-tertiary-butylamine:ti,ab
#49 Ionamin:ti,ab
#50 adipex-P:ti,ab
#51 anoxine-AM:ti,ab
#52 duromine:ti,ab
#53 metermine:ti,ab
#54 mirapron:ti,ab
#55 obephen:ti,ab
#56 obestin-30:ti,ab
#57 phentremene:ti,ab
#58 phentrol:ti,ab
#59 phenterex:ti,ab
#60 phentromin:ti,ab
#61 "pro-fast SA":ti,ab
#62 redusa:ti,ab
#63 panbesy:ti,ab
#64 "phentermine trenker":ti,ab
#65 Obenix:ti,ab
#66 Oby-trim:ti,ab
#67 Tera mine:ti,ab
#68 Zantryl:ti,ab
#69 Sinpet:ti,ab
#70 Supremin:ti,ab
#71 Umine:ti,ab
#72 Weltmine:ti,ab
Lifestyle interventions for acute gout (Review)

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Appendix 2. MEDLINE search strategy

1. exp gout/
2. gout$.tw.
3. 1 or 2
4. exp life style/
5. (life adj2 (style$ or change$ or event$)).tw.
6. lifestyle$.tw.
7. social support/
8. social support.tw.
9. exp relaxation/ or relaxation therapy/
10. relax$.tw.
11. self efficacy/
12. (self adj (efficac$ or help or manag$ or care$)).tw.
13. exp health promotion/
14. exp health education/
15. (health adj (promot$ or educat$)).tw.
16. (motivat$ adj (therap$ or interview$)).tw.
17. or/4-16
18. exp Weight Loss/
19. weight loss.tw.
20. (weight adj2 (lo$ or reduc$ or eliminat$)).tw.
21. ((body mass index or bmi) adj3 (los$ or reduc$ or decreas$ or low$)).tw.
22. (Waist circumference adj2 (reduc$ or low$ or small$)).tw.
23. (Waist size adj2 (reduc$ or low$ or small$)).tw.
24. energy restrict$.tw.
25. (calor$ adj2 (restrict$ or reduc$ or low$)).tw.
26. exp Anti-Obesity Agents/
27. (appetite adj2 suppress$).tw.
28. orlistat.tw.
29. xenical.tw.
30. alli.tw.
31. tetrahydrolipstatin.tw.
32. phentermine.tw.
33. phenyl-tertiary-butylamine.tw.
34. Ionamin.tw.
35. adipex-P.tw.
36. anxione-AM.tw.
37. duromine.tw.
38. metermine.tw.
39. mirapront.tw.
40. obephen.tw.
41. obephen-30.tw.
42. phentremene.tw.
43. phentrol.tw.
44. phenterex.tw.
45. phentromin.tw.
46. pro-fast SA.tw.
Lifestyle interventions for acute gout (Review)

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Appendix 3. EMBASE search strategy

1. exp gout/
2. gout$.tw.
3. 1 or 2
4. exp life style/
5. Lifestyle modification/
6. (life adj2 (style$ or change$ or event$)).tw.
7. lifestyle$.tw.
8. Social support/
9. social support.tw.
10. Relaxation training/
11. relax$.tw.
12. Self concept/ or exp self care/
13. (self adj (efficac$ or help or manag$ or care$)).tw.
14. Health promotion/
15. exp health education/
16. (health adj (promot$ or educat$)).tw.
17. (motivat$ adj (therap$ or interview$)).tw.
18. 4 or 17
19. weight reduction/
20. (weight adj2 (los$ or reduc$ or eliminat$)).tw.
21. ((body mass index or bmi) adj3 (los$ or reduc$ or decreas$ or low$)).tw.
22. (Waist circumference adj2 (reduc$ or low$ or small$)).tw.
23. (Waist size adj2 (reduc$ or low$ or small$)).tw.
24. energy restrict$.tw.
25. (calor$ adj2 (restrict$ or reduc$ or low$)).tw.
26. antiobesity agent/
27. (appetite adj2 suppress$).tw.
28. orlistat.tw.
29. xenical.tw.
30. alli.tw.
31. tetrahydrolipstatin.tw.
32. phentermine.tw.
33. phenyl-tertiary-butylamine.tw.
34. Ionamin.tw.
35. adipex-P.tw.
36. anoxine-AM.tw.
37. duromine.tw.
38. metermin.tw.
39. mirapront.tw.
40. obepehn.tw.
41. obestin-30.tw.
42. phentremene.tw.
43. phentrol.tw.
44. phenterex.tw.
45. phentromin.tw.
46. pro-fast SA.tw.
47. redusa.tw.
48. panbesy.tw.
49. phentermine trenker.tw.
50. Obenix.tw.
51. Oby-trim.tw.
52. Teramine.tw.
53. Zantryl.tw.
54. Sinpet.tw.
55. Supremin.tw.
56. Umine.tw.
57. Weltmine.tw.
58. amfebutamone/
59. Aplenzin.tw.
60. Zyban.tw.
61. or/19-60
62. exp diet/
63. diet$.tw.
64. exp diet therapy/
65. (lacto-vegetarian$ or lacto vegetarian$ or vegetarian$ or non-vegetarian$).tw.
66. (non adj2 vegetarian$).tw.
67. vegan$.tw.
68. (Cretan or Mediterranean).tw.
69. fast$.tw.
70. (protein adj2 (restrict$ or reduc$ or low$ or elim$)).tw.
71. (purine adj2 (restrict$ or reduc$ or low$ or elim$)).tw.
72. (fat adj2 (restrict$ or reduc$ or low$ or elim$)).tw.
73. (triglyceride adj2 (restrict$ or reduc$ or low$ or elim$)).tw.
74. (cholesterol adj2 (restrict$ or reduc$ or low$ or elim$)).tw.
75. or/62-73
76. exp dairy product/
77. (milk or cheese$ or yog?urt or dairy).tw.
78. milk/
79. or/76-78
80. sucrose/
81. fructose/
82. (sucrose$ or lactose$ or glucose$ or fructose$ or glycerine$ or lycerine$ or dextrose$ or aspartame$ or polyrose$ or sacchar$ or sugar$).tw.
83. (sweet$ adj6 (solution$ or tast$)).tw.
84. (Diet$ adj3 (drink$ or beverage$)).tw.
85. (soft adj2 (drink or beverage)).tw.
86. (sugar adj2 free adj2 (drink$ or beverage$)).tw.
87. (soda or sodas).tw.
88. or/80-87
89. coffee/
90. caffeine/
91. (coffee or caffiene or caffeinated or decaffeinated).tw.
92. or/89-91
93. alcohol/
94. ethanol.tw.
95. alcoholism/
96. drinking behavior/
97. alcohol$.tw.
98. or/93-97
99. exp exercise/
100. exp kinesiotherapy/
101. physical education/
102. fitness/
103. exp sports/
104. exercis$.tw.
105. sport$.tw.
106. (physical$ adj (fit$ or exert$ or activ$)).tw.
107. (run$ or jog$ or walk$).tw.
108. (swim$ or cycl$ or bicycl$).tw.
109. train$.tw.
110. kinesi?therap$.tw.
111. ((weight or muscle$) adj (strength$ or resistance)).tw.
112. endurance.tw.
113. or/99-112
114. tobacco/
115. tobacco dependence/
116. smoking cessation/
117. exp "smoking and smoking related phenomena"/
118. nicotine/
119. smok$.tw.
120. (cigarette$ or cigar$ or pipe$).tw.
121. nicotine replacement therapy/
122. (nicotine adj (replacement or patch$ or gum or nasal)).tw.
123. nrt.tw.
124. nicorette.tw.
125. Nicotrol.tw.
126. Nicoderm$.tw.
127. Habitrol.tw.
128. amfebutamone/
129. Bupropion.tw.
130. Amfebutamone.tw.
131. Aplenzin.tw.
132. Budeprion.tw.
133. Buproban.tw.
134. Butrew.tw.
135. Buxon.tw.
136. champix.tw.
CONTRIBUTIONS OF AUTHORS

JM wrote the current version of the protocol. RB, CE and MS provided comments and suggestions on draft versions of the protocol, and all authors approved the current version.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT
Internal sources

- The Royal Melbourne Hospital, Australia.
  In kind support
- Monash University, Australia.
  In kind support
- Cabrini Hospital, Australia.
  In kind support
- Southampton General Hospital, UK.
  In kind support

External sources

- No sources of support supplied, Not specified.