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Lifestyle modifications for non-alcohol related fatty liver disease: a network meta-analysis (Protocol)

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Lifestyle modifications for non-alcohol related fatty liver disease: a network meta-analysis.
Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD013156.
DOI: 10.1002/14651858.CD013156.

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[Intervention Protocol]

Lifestyle modifications for non-alcohol related fatty liver disease: a network meta-analysis

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 10, 2018.

Citation: Gurusamy KS, Tsochatzis E, Madden AM. Lifestyle modifications for non-alcohol related fatty liver disease: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 10. Art. No.: CD013156. DOI: 10.1002/14651858.CD013156.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the comparative benefits and harms of different lifestyle interventions in the treatment of non-alcohol related fatty liver disease.

BACKGROUND

Description of the condition

Fatty liver disease is steatosis (accumulation of fat, usually triglycerides) in the parenchymal cells of the liver (NCBI 2018). Non-alcohol related fatty liver disease (also called non-alcoholic fatty liver disease (NAFLD)) is liver steatosis in the absence of significant alcohol consumption; use of medications such as methotrexate, tamoxifen, or steroids; or other disorders that result in fat accumulation, such as hepatitis C virus infection, Wilson's disease, starvation, and lecithin cholesterol acyltransferase (LCAT) deficiency (Angulo 2002; Chalasani 2012). Fatty liver disease includes a spectrum of disorders ranging from simple steatosis or non-alcoholic fatty liver (NAFL) (fat accumulation without evidence of injury to the parenchymal cells of the liver), non-alcoholic steatohepatitis (NASH) (fat accumulation with injury to the liver's parenchymal cells but without cirrhosis), to NASH cirrhosis (advanced liver fibrosis with current or previous NAFL or NASH) (Chalasani 2012; Rinella 2015). However, it has to be noted that the existing non-invasive tests to distinguish NAFLD from alcohol-related liver disease (ALD) are only about 75% to 90% accurate and some patients with ALD may be misclassified as NAFLD (Cerovic 2013; Wang 2016).

The prevalence of NAFLD varies between 19% and 33% in different populations, depending upon ethnicity, region of origin (also among people of similar ethnicity), being overweight or obese, and having other disorders such as diabetes mellitus or hypertension (Bedogni 2005; Park 2006; Dassanayake 2009; Koehler 2012; Lazo 2013; Fleischman 2014; Li 2014; Shen 2014; Nishioji 2015). The major risk factors associated with increased prevalence of NAFLD are obesity, being male, increasing age, ethnicity (e.g. Mexican-Americans have higher prevalence of fatty liver than other ethnic groups), genetic susceptibility (e.g. genetic variation in patatin-like phospholipase domain containing 3 gene), hypertension, hypercholesterolaemia, diabetes mellitus, lower so-

cioeconomic status, lower level educational attainment, poor sleep pattern, and lower physical activity (Bedogni 2005; Park 2006; Dassanayake 2009; Sookoian 2011; Koehler 2012; Lazo 2013; Fleischman 2014; Shen 2014; Bernsmeier 2015; Lonardo 2015). The mean age of people with NAFLD varies between 40 years and 60 years (Bedogni 2005; Dassanayake 2009; Shen 2014). In studies with long-term follow-up, the mean age of people with NAFLD has ranged between 45 years and 50 years (Adams 2005; Bedogni 2007; Soderberg 2010; Onnerhag 2014). After a mean follow-up period of eight to 28 years, the presence of NAFLD increased overall long-term mortality compared to the general population without NAFLD (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; Onnerhag 2014).

People with NAFLD are at risk of dying before reaching the mean life expectancy at birth (Adams 2005; Bedogni 2007; Ong 2008; Soderberg 2010; Onnerhag 2014). It is widely believed that people with simple steatosis rarely progress to advanced liver disease, but people with NASH may develop cirrhosis (Chalasani 2012). It has been reported that in people with NAFLD, liver fibrosis was the only histological feature associated with increased mortality and requirement for liver transplantation (Angulo 2015; Ekstedt 2015). In a study that followed people with simple steatosis and NASH for a mean of 28 years, similar rates of mortality were observed between participants with simple steatosis and those with NASH, but higher mortality rates were observed in people with severe fibrosis regardless of whether they had bland steatosis (steatosis without inflammation) or NASH (Soderberg 2010). It is noteworthy that NAFLD is associated with metabolic syndrome, that is, presence of three of the following factors: hypertension, raised triglycerides, lowered high-density lipoprotein cholesterol, raised fasting glucose, and central obesity (Alberti 2009; Ballestri 2016). Therefore, increased mortality in people with NAFLD may be related to metabolic syndrome, rather than NAFLD alone. Furthermore, ALD has worse prognosis that NAFLD (Dam-Larsen 2005); the difficulty in distinguishing NAFLD from ALD may also contribute to the higher mortality observed in NAFLD.

Non-alcohol related fatty liver disease is currently one of the most common causes of liver transplantation: since 2008, NAFLD has been either the second or third most common reason for liver transplantation each year, and the number of people who underwent liver transplantation for NAFLD has been similar to that of alcohol-related liver disease since 2008 (Cholankeril 2017). The risk of hepatocellular carcinoma (HCC), the most common type of primary liver cancer in adults, is higher in people with NASH cirrhosis compared to people with NAFLD without cirrhosis and the general population: approximately 2% to 13% of people with NASH cirrhosis develop HCC in three to seven years (White 2012). However, HCC can occur in people with NAFLD without them having cirrhosis (Piscaglia 2016).

Fat accumulates within the liver cells when there is an imbalance between the mechanisms that reduce fat in cells (such as oxidation of fatty acids or secretion of lipoproteins) and mechanisms that increase fat in cells (such as increased uptake of fat and increased production of fat). The accumulation of fat leading to NAFLD is believed to be mediated by insulin resistance, because insulin resistance increases the breakdown of peripheral adipose tissue which results in increased influx of free fatty acids (FFA), promotes the synthesis of new triglycerides within the liver, and decreases the oxidation of FFAs (Abdelmalek 2007; Buzzetti 2016). The accumulation of fat in the liver causes injury due to pro-inflammatory cytokines (Riley 2007). However, the mechanism by which only a proportion of people develop advanced liver fibrosis or primary liver cancer (hepatocellular cancer or HCC) is unclear (Abdelmalek 2007). A 'multiple parallel hits' model - involving nutrition, gut bacteria, and accumulation of fat leading to liver inflammation - has been proposed to explain the development and progression of NAFLD (Tilg 2010).

Ultrasound is a widely used method for screening the general population for NAFLD; however, it is operator-dependent (Hernaez 2011), and may miss 15 people with fatty liver disease out of every 100 people screened (Hernaez 2011). It may also yield false-positive results in seven out of 100 people without fatty liver disease (Hernaez 2011). While liver biopsy can be considered the definitive investigation to confirm the diagnosis, it is invasive and not suitable for screening the general population.

Description of the intervention

Various interventions have been tried in the treatment of people with NAFLD. This review will examine lifestyle modifications such as dietary changes and/or increased physical activity (Abenavoli 2015; Shojaee-Moradie 2016; Zhang 2016; Houghton 2017) (the focus of the present systematic review). Other interventions not included in this review include nutritional supplementation (probiotics, prebiotics, synbiotics, vitamin supplementation, polyunsaturated fatty acid supplementation) (Nabavi 2014; Sharifi 2014; Li 2015; Nogueira 2016; Mofidi 2017); pharmacological interventions (Lombardi 2017); and weight reduction surgery (bariatric surgery) in obese people with NAFLD (Adorini 2012; Anstee 2012; Chalasani 2012; Paschos 2012; Abenavoli 2013a). While liver biopsy can be considered the definitive investigation to confirm the diagnosis, it is invasive and not suitable for screening the general population.

How the intervention might work

Lifestyle modifications, such as dietary changes and increased physical activity, are aimed at decreasing weight and serum lipid profile (Abenavoli 2015; Shojaee-Moradie 2016; Zhang 2016; Houghton 2017). This may lead to resolution or decrease the progression of fatty liver disease (Chalasani 2012). Dietary modifications may also decrease insulin resistance and increase antioxidants, leading to improvement in NAFLD, and improve the vitamins and

other micronutrients available naturally from the food (Conlon 2013). Poor sleep pattern is associated with an increased risk of NAFLD due to its correlation with insulin resistance (Bernsmeier 2015). Lifestyle interventions aimed at improving sleep pattern may therefore improve NAFLD by decreasing insulin resistance. Nutritional supplementation (not included in this review) may work in different ways: vitamin E decreases oxidative damage to liver cells (Chalasani 2012); the effect of vitamin D supplementation may be mediated through its ability to decrease inflammatory markers and lipid peroxidation (Sharifi 2014), that of probiotics may be mediated through its ability to decrease inflammatory markers and alter lipid profile (Al-Muzafar 2017), and that of polyunsaturated fatty acids may be mediated through ability to alter lipid profile (Chalasani 2012). This may lead to resolution or decrease progression of fatty liver disease. There is currently no effective pharmacological intervention in people with NAFLD or NASH; however, there is significant uncertainty about the effect of pharmacological interventions on NAFLD (Lombardi 2017). The reasons for investigating these pharmacological interventions (not included in this review) have been based on their potential to decrease weight, insulin resistance, and/or oxidative damage to liver cells, alter lipid profile, or their anti-inflammatory and anti-fibrotic properties (Adorini 2012; Anstee 2012; Chalasani 2012; Thoma 2012; Abenavoli 2013a). Surgeries resulting in weight loss (not included in this review) may improve fatty liver by reducing weight (Chalasani 2012).

Why it is important to do this review

Currently, there is no effective pharmacological treatment for NAFLD with or without NASH (Lombardi 2017). Research on treatments to decrease NAFLD and NASH have been identified as top research priorities by patients, carers, and healthcare professionals involved in the treatment of liver diseases in UK (Gurusamy 2018a). Lifestyle modifications have the potential to result in resolution or to decrease the progression of fatty liver disease. Network meta-analysis enables direct and indirect evidence to be combined, and different interventions to be ranked in terms of different outcomes (Salanti 2011; Salanti 2012). There has been no previous Cochrane Review on this topic. Therefore, it is important to assess the benefits and harms of lifestyle modifications in the treatment of people with NAFLD. If it is not possible to perform this review using network meta-analysis methods, for example, if the transitivity assumption (please see below) is unlikely to be met, we will instead use standard Cochrane methods to perform meta-analysis of head-to-head comparisons whenever possible. We will also present results from direct comparisons whenever possible, even if we perform the network meta-analysis.

OBJECTIVES

To assess the comparative benefits and harms of different lifestyle interventions in the treatment of non-alcohol related fatty liver disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider only randomised clinical trials for this network meta-analysis, irrespective of language, publication status, or date of publication. We will exclude studies of other designs because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events. It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, because of the exponentially increased amount of work required to include non-randomised studies, we will exclude them from the current review. We will register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events if there is uncertainty in the balance of benefits and harms of effective treatment(s).

Types of participants

We will include randomised clinical trials with participants who have non-alcohol related fatty liver disease (NAFLD), irrespective of the method of diagnosis, age and diabetic status of participants, or presence of non-alcoholic steatohepatitis (NASH). We will exclude randomised clinical trials in which participants have previously undergone liver transplantation.

Types of interventions

We will include any of the following interventions for comparison with one another, either alone or in combination.

- Supervised physical activity (for example, exercise classes)
- General physical activity advice
- Rationed diet (for example, daily or weekly rations of different foods, calorie restricted diet)
- Special diets (for example, Mediterranean diet, Atkin's diet, high-fibre diet, or diet with high fruit and vegetable content)
- General dietary advice (for example, information on the fat or carbohydrate content of different foods)
- Lifestyle modifications that promote sleep (for example, nicotine and caffeine restriction)

- No active intervention (including sham or placebo interventions).

We will include trials in which the above interventions were combined with other interventions aimed at decreasing NAFLD (but will consider these as potential effect modifiers), provided that these cointerventions are administered equally in both arms. We will include nutritional supplements (in form of tablets, powder, or solution) in a different review (Gurusamy 2018b).

We will evaluate the plausibility of the transitivity assumption (the assumption that participants included in the different trials with different treatments for NAFLD can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions) (Salanti 2012), by looking at the inclusion and exclusion criteria in the studies. In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect-modifiers such as diabetic status and cointerventions status are similar across trials. If there is any concern about the transitivity assumption, we will perform separate meta-analysis for each of these different types of participants.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death).
- Health-related quality of life, as defined in the included trials, using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018) at maximal follow-up.
- Serious adverse events (during or within six months after cessation of intervention). We define a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, we will use the definitions used by study authors for serious adverse events.
    - Proportion of trial participants with one or more serious adverse event
    - Number of serious adverse events per participant

Secondary outcomes

- Any adverse events (during or within six months after cessation of intervention). We define an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of intervention) (ICH-GCP 1997). However, we will use the definition used by study authors for adverse events.
    - Proportion of trial participants with any adverse events
    - Number of any adverse events per participant
- Time to liver transplantation (maximal follow-up)
- Time to decompensation (maximal follow-up)
- Time to cirrhosis (maximal follow-up)

Exploratory outcomes

- Time to resolution of fatty liver disease (maximal follow-up)
- Fibrosis score at maximal follow-up
- NAFLD activity score

We have chosen outcomes based on:

- their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2018a);
- feedback from the patient and public representative of this project; and
- an online survey about the outcomes promoted through the Cochrane Consumer Network.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science), from inception to date of search, for randomised clinical trials comparing two or more of the above interventions, without applying any language restrictions (Royle 2003). We will search for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we will also search clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) which searches various trial registers, including ISRCTN and ClinicalTrials.gov. We will also search the European Medical Agency (EMA) (www.ema.europa.eu/ema/) and US Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. The provisional search strategies are provided in Appendix 1. To improve efficiency in study selection, this review will share the same search strategy as another review on nutritional supplementation in people with NAFLD (Gurusamy 2018b).

Searching other resources

To identify additional trials for inclusion, we will search the references of the identified trials and the existing Cochrane Reviews on non-alcohol related fatty liver disease.

Data collection and analysis

Selection of studies

Two review authors (KG and a research assistant) will independently identify trials for inclusion by screening the titles and abstracts and will seek full-text articles for any references identified by at least one of the review authors for potential inclusion. We will select trials for inclusion based on the full-text articles. We will provide the list of references that we excluded and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We will also list any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We will resolve any discrepancies through discussion.

Data extraction and management

Two review authors (KG and a research assistant) will independently extract the following data using a piloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - natural logarithm of hazard ratio and its standard error, if this was reported, rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used, if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, diabetic status, method of diagnosis, presence of NASH;
  - details of the intervention and control (including intensity (for exercise interventions) (CDC 2018), or type of diet (for example, low-fat diet, high-protein diet, Mediterranean diet), frequency, and duration);
  - length of follow-up;
  - information related to 'Risk of bias' assessment (please see below).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria.

We will collect outcomes at maximum follow-up but also at short term (up to three months) and medium term (from three months to five years) if these data are available.

We will contact the trial authors in the case of unclear or missing information. If there is any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we will attempt to contact the trial authors to clarify whether the trial report was duplicated. Any differences in opinion will be resolved through discussion.

Assessment of risk of bias in included studies

We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2018) to assess the risk of bias in included trials. Specifically, we will assess sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the study. In general, we will classify the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (for example, use of interactive voice response system).
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators are unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will exclude such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel was attempted, but it was likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; or blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but it was likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for treatment of people with NAFLD, namely, all-cause mortality or resolution of NAFLD, along with adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes will not be considered to be reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or results of the trial (industry-sponsored trials overestimate the efficacy by about 25%) (Lundh 2017).
- Uncertain risk of bias: the trial may or may not have been free of for-profit bias, as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Uncertain risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. baseline differences, early stopping).

We will consider a trial to be at low risk of bias if we assess the trial to be at low risk of bias across all domains listed above. Otherwise, we will consider trials to be at high risk of bias. At the outcome level, we will classify an outcome to be at low risk of bias if the allocation sequence generation, allocation concealment, blinding of participants, healthcare professionals, and outcome assessors, incomplete outcome data, and selective outcome reporting (at the outcome level) are at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we will calculate the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we will calculate the mean difference (MD) with 95% CrI. We will use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials use different scales. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we will calculate the rate ratio (RaR) with 95% CrI. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we will calculate the hazard ratio (HR) with 95% CrI.

Relative ranking

We will estimate the ranking probabilities for all interventions of being at each possible rank for each intervention. We will obtain the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis will be the participant undergoing treatment for NAFLD, according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

We will include cluster-randomised clinical trials provided that the effect estimate adjusted for cluster correlation is available, or if there is sufficient information to calculate the design effect from the trial, as this will allow us to take clustering into account. We will also assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Cross-over randomised clinical trials

If we identify any cross-over randomised clinical trials, we will include the outcomes after the period of first intervention, because the included treatments can have residual effects.

Trials with multiple intervention groups

We will collect data for all trial intervention groups that meet the inclusion criteria. The codes for analysis that we will use, will account for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We will perform an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we will use the data available to us. This may result in the use of 'per-protocol' analyses. Since these may be biased, particularly if the data are not missing at random (for example, the treatment was withdrawn due to adverse events, or the duration of treatment was shortened because of lack of response and such participants were excluded from analysis), we will conduct best-worst case scenario analysis (which assumes a good outcome in the intervention group and bad outcome in the control group) and worst-best case scenario analysis (which assumes a bad outcome in the intervention group and a good outcome in the control group) as sensitivity analyses whenever possible for dichotomous outcomes.

For continuous outcomes, we will impute the standard deviation from P values according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data are likely to be normally distributed, we will use the median for meta-analysis when the mean is not available. If it is not possible to calculate the standard deviation from the P value or the confidence intervals, we will impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates for various subgroups (please see Subgroup analysis and investigation of heterogeneity). Different study designs and risk of bias can also contribute to methodological heterogeneity.

We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2, and comparing this with values reported in study of the distribution of between-study heterogeneity) (Turner 2012), and by calculating I^2 using Stata/SE 14.2. If we identify substantial clinical, methodological, or statistical heterogeneity, we will explore and address the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We will assess the transitivity assumption by comparing the distribution of the following potential effect modifiers across the different pairwise comparisons.

- Clinical: people with and without diabetes, people with and without NASH, different types of exercises/diets, and based on the cointerventions.

- Methodological: risk of bias, year of randomisation, duration of follow-up).

Assessment of reporting biases

For the network meta-analysis, we will perform a comparison-adjusted funnel plot. If there is no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we will judge the reporting bias by the completeness of the search (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We will obtain a network plot to ensure that the trials are connected by interventions using Stata/SE 14.2 (Chaimani 2013). We will exclude any trials that are not connected to the network from the network meta-analysis and report only the direct pairwise meta-analysis for such comparisons. We will summarise the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters'), using appropriate likelihood functions and links (Lu 2006). We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of 'at risk' individuals at the point when they are censored), and normal likelihood and identity link for continuous outcomes. We will use 'no active intervention' as the reference group. We will use a fixed-effect model and random-effects model for the network meta-analysis. We will report both models for comparison with the reference group in a forest plot. For each pairwise comparison in a table, we will report the fixed-effect model if the two models report similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values, employing codes provided by the NICE DSU (Dias 2016). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: zero to five) for between-trial standard deviation but will assume the same between-trial standard deviation across treatment comparisons (Dias 2016). We will use a 'burn-in' of 10,000 simulations, check for convergence (of effect estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mix very well by visualisation), and run the models for another 10,000 simulations to obtain effect estimates. If we do not obtain convergence, we will increase the number of simulations for the 'burn-in'. If we still do not obtain convergence, we will use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We will estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use inconsistency models employed in the NICE DSU manual, as we will use a common between-study standard deviation (Dias 2014). In addition, we will use design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013). We will use Stata/SE 14.2 to create IF plots. In the presence of inconsistency, we will assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in Subgroup analysis and investigation of heterogeneity.

If there is evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparisons

We will perform the direct comparisons using the same codes and the same technical details as described above.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 2. We will perform Trial Sequential Analysis for direct comparisons to control the risk of random errors when at least two trials are included for the comparison of other interventions versus no active intervention ('control'), for the outcomes all-cause mortality at

maximal follow-up and health-related quality of life, the two outcomes that determine whether the intervention should be given (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). For all-cause mortality at maximal follow-up, we will use an alpha error according to the guidance of Jakobsen 2014 (i.e. 0.033), power of 90% (beta error of 10%) (Castellini 2017), a relative risk reduction of 20%, the median control group proportion observed in the trials, and the heterogeneity observed in the meta-analysis using Stata/SE 14.2, employing methods suggested by Miladinovic and colleagues (Miladinovic 2013). For health-related quality of life, a continuous outcome, we will use an alpha error according to the guidance of Jakobsen 2014 (i.e. 0.033), power of 90% (beta error of 10%) (Castellini 2017), a standardised mean difference of 0.2, the median health-related quality of life in the control group in the trials, and the heterogeneity observed in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We plan to assess the differences in the effect estimates between the following subgroups, and to investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in the NICE DSU guidance if we include a sufficient number of trials (Dias 2012a). We plan to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias.
- Participants with NASH compared to participants with NAFLD but without NASH.
- Participants with diabetes mellitus compared to participants without diabetes mellitus.
- Different types of exercises/diets.
- Cointerventions (for example, both groups receive omega-3 fatty acid supplementation).
- Period of follow-up (short term: up to three months; medium term: more than three months to five years; long-term: more than five years).
- Definition used by authors for serious adverse events and any adverse events (ICH-GCP 1997 criteria versus other definitions).

We will calculate a single common interaction term when applicable (Dias 2012a). If the 95% CrI of the interaction term does not overlap zero, we will consider this to represent statistically significant heterogeneity.

Sensitivity analysis

If a trial reports only per-protocol analysis results, we plan to re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible. We will also perform a sensitivity analysis excluding the trials in which mean or standard deviation, or both, were imputed and use the median standard deviation in the trials to impute missing standard deviations.

We will compare our assessments of imprecision with GRADE methodology to that with Trial Sequential Analysis methodology (Castellini 2018).

Presentation of results

We will follow the PRISMA-NMA statement while reporting (Hutton 2015). We will present the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We will plot the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b). We will also provide the CrI of the probabilities in the ranking probability tables. We will upload all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo) and provide a link within the review.

Grading of evidence

We will present 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We will follow the approach suggested by Puhan and colleagues (Puhan 2014). First, we will calculate the direct and indirect effect estimates and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions, and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions. Next we will rate the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). We will then present the estimates of the network meta-analysis and rate the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, we will present information on the absolute measures (i.e. proportion of people with the outcome in each intervention group based on the direct estimates, indirect estimates, and network meta-analysis estimates). We will also present information on the number of trials and participants, according to the format of standard 'Summary of findings' tables.

Recommendations for future research

We will provide recommendations for future research in the population, intervention, control, outcomes, period of follow-up, and study design based on the uncertainties that we identify from the existing research.

ACKNOWLEDGEMENTS

We acknowledge the help and support of the Cochrane Hepato-Biliary Group. The authors would also like to thank the people listed below who provided comments to improve the protocol.

Peer reviewers: Somaya Albhaisi, USA; Mario Marasone, Italy; Ludovico Abenavoli, Italy

Contact Editor: Christian Gluud, Denmark

Sign-off Editor: Christian Gluud, Denmark

Cochrane Review Group funding acknowledgement: The Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark.

This project was funded by the National Institute for Health Research Systematic Reviews Programme (project number 16/114/17).

Department of Health Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the 16/114/17 Programme, NIHR, NHS or the Department of Health.

Danish State and The Copenhagen Trial Unit Disclaimer

The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Fatty Liver] explode all trees #2 (liver and (fatty or steatosis or steatoses)) #3 NAFLD #4 #1 or #2 or #3 #5 (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria) #6 MeSH descriptor: [Dietary Supplements] explode all trees #7 (vitamin* or micronutrient* or (trace near/1 (element* or mineral*)) or antioxidant*) #8 MeSH descriptor: [Vitamins] explode

(*Continued*)

		all trees #9 MeSH descriptor: [Micronutrients] explode all trees #10 MeSH descriptor: [Antioxidants] explode all trees #11 (((unsaturated or polyunsaturated) and (fatty near/1 acid*)) or PUFA or (linoleic near/1 acid*) or (docosahexaenoic near/1 acid*) or (eicosapentaenoic near/1 acid)) #12 MeSH descriptor: [Fatty Acids, Unsaturated] explode all trees #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 MeSH descriptor: [Exercise] this term only #15 MeSH descriptor: [Exercise Therapy] this term only #16 MeSH descriptor: [Physical Exertion] this term only #17 MeSH descriptor: [Motor Activity] this term only #18 MeSH descriptor: [Sports] this term only #19 (sport*) #20 MeSH descriptor: [Physical Education and Training] explode all trees #21 (physical near/3 (activit* or education* or exertion* or training)) #22 (exercise*) #23 MeSH descriptor: [Diet Therapy] explode all trees #24 ((diet or dieting) near/5 (health* or weight*)) #25 (calorie near/3 (control or reduc* or restriction)) #26 "food choice*" #27 ("fat camp*" or "weight loss camp*") #28 "nutrition education" #29 MeSH descriptor: [Nutrition Therapy] this term only #30 MeSH descriptor: [Behavior Therapy] this term only #31 MeSH descriptor: [Cognitive Therapy] this term only #32 MeSH descriptor: [Psychotherapy] this term only #33 (behavio?r* near/3 (therap* or tech-

(*Continued*)

		nique* or modif* or intervention*)) #34 (cognit* near/3 (therap* or technique* or modif* or intervention*)) #35 CBT #36 (psychotherap* or psycho-therap*) #37 (psycho-social or psychosocial) #38 MeSH descriptor: [Health Promotion] explode all trees #39 MeSH descriptor: [Health Education] this term only #40 (health* near/3 (promot* or educat* or lifestyle)) #41 MeSH descriptor: [Life Style] this term only #42 (lifestyle* or life-style*) #43 #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 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 #44 #13 or #43 #45 #4 and #44
MEDLINE Ovid	January 1947 to date of search	1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized.ab. 4. placebo.ab. 5. drug therapy.fs. 6. randomly.ab. 7. trial.ab. 8. groups.ab. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp animals/ not humans.sh. 11. 9 not 10 12. exp Fatty Liver/ 13. (liver and (fatty or steatosis or steatoses)).ti,ab. 14. NAFLD.ti,ab. 15. 12 or 13 or 14 16. (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria).ti,ab. 17. exp Dietary Supplements/ 18. (vitamin* or micronutrient* or (trace adj1 (element* or mineral*)) or antioxidant*).ti,ab. 19. exp Vitamins/ or exp MICRONUTRI-

(*Continued*)

		ENTS/ or exp ANTIOXIDANTS/ 20. (((unsaturated or polyunsaturated) and (fatty adj1 acid*)) or PUFA or (linoleic adj1 acid*) or (docosahexaenoic adj1 acid*) or (eicosapentaenoic adj1 acid)).ti,ab. 21. exp Fatty Acids, Unsaturated/ 22. 16 or 17 or 18 or 19 or 20 or 21 23. Exercise/ or Exercise Therapy/ or Physical Exertion/ or Motor Activity/ or Sports/ 24. sport*.tw. 25. exp "Physical Education and Training"/ 26. (physical adj3 (activit* or education* or exertion* or training)).tw. 27. exercise*.tw. 28. exp diet therapy/ 29. ((diet or dieting) adj5 (health* or weight*)).tw. 30. (calorie adj3 (control or reduc* or restriction)).tw. 31. food choice*.tw. 32. (fat camp* or weight loss camp*).tw. 33. nutrition education.tw. 34. Nutrition Therapy/ or behavior therapy/ or Cognitive Therapy/ or psychotherapy/ 35. (behavio?r* adj3 (therap* or technique* or modif* or intervention*)).tw. 36. (cognit* adj3 (therap* or technique* or modif* or intervention*)).tw. 37. CBT.tw. 38. (psychotherap* or psycho-therap*).tw. 39. (psycho-social or psychosocial).tw. 40. exp Health Promotion/ or Health Education/ 41. (health* adj3 (promot* or educat* or lifestyle)).tw. 42. lifestyle/ 43. (lifestyle* or life-style*).tw. 44. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 45. 22 or 44 46. 11 and 15 and 45
Embase Ovid	January 1974 to date of search	1. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 2. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*)

(*Continued*)

		or assign* or allocat* or volunteer*).af. 3. 1 or 2 4. exp fatty liver/ 5. (liver and (fatty or steatosis or steatoses)).ti,ab. 6. NAFLD.ti,ab. 7. 4 or 5 or 6 8. (((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacteria).ti,ab. 9. exp dietary supplement/ or probiotic agent/ or prebiotic agent/ or synbiotic agent/ 10. (vitamin* or micronutrient* or (trace adj1 (element* or mineral*)) or antioxidant*).ti,ab. 11. exp vitamin/ or exp trace element/ or exp antioxidant/ 12. (((unsaturated or polyunsaturated) and (fatty adj1 acid*)) or PUFA or (linoleic adj1 acid*) or (docosahexaenoic adj1 acid*) or (eicosapentaenoic adj1 acid)).ti,ab. 13. exp polyunsaturated fatty acid/ 14. 8 or 9 or 10 or 11 or 12 or 13 15. exercise/ or kinesiotherapy/ or motor activity/ or sport/ 16. sport*.tw. 17. (physical adj3 (activit* or education* or exertion* or training)).tw. 18. exercise*.tw. 19. exp diet therapy/ 20. ((diet or dieting) adj5 (health* or weight*)).tw. 21. (calorie adj3 (control or reduc* or restriction)).tw. 22. food choice*.tw. 23. (fat camp* or weight loss camp*).tw. 24. nutrition education.tw. 25. behavior therapy/ or Cognitive Therapy/ or psychotherapy/ 26. (behavio?r* adj3 (therap* or technique* or modif* or intervention*)).tw. 27. (cognit* adj3 (therap* or technique* or modif* or intervention*)).tw. 28. CBT.tw. 29. (psychotherap* or psycho-therap*).tw.

(*Continued*)

		30. (psycho-social or psychosocial).tw. 31. exp Health Promotion/ or Health Education/ 32. (health* adj3 (promot* or educat* or lifestyle)).tw. 33. lifestyle/ or lifestyle modification/ 34. (lifestyle* or life-style*).tw. 35. 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 or 32 or 33 or 34 36. 14 or 35 37. 3 and 7 and 36
Science Citation Index Expanded (Web of Science)	January 1945 to date of search	#1 TS = ((liver and (fatty or steatosis or steatoses)) or NAFLD) #2 TS=(((Diet* or nutrition* or food*) and Supplement*) or nutraceutical* or nutriceutical* or neutraceutical* or probiotic* or prebiotic* or synbiotic* or lactobacill* or bifidobacterial or vitamin* or micronutrient* or (trace near1 (element* or mineral*)) or ((unsaturated or polyunsaturated) and (fatty near1 acid*)) or antioxidant* or PUFA or (linoleic near1 acid*) or (docosahexaenoic near1 acid*) or (eicosapentaenoic near1 acid)) #3 TS=(sport* or (physical near/3 (activit* or education* or exertion* or training)) or exercise* or ((diet or dieting) near/5 (health* or weight*)) or (calorie near/3 (control or reduc* or restriction)) or "food choice*" or "fat camp*" or "weight loss camp*" or "nutrition education" or (behavio?r* near/3 (therap* or technique* or modif* or intervention*)) or (cognit* near/3 (therap* or technique* or modif* or intervention*)) or CBT or psychotherap* or psycho-therap* or psycho-social or psychosocial or (health* near/3 (promot* or educat* or lifestyle)) or lifestyle* or life-style* or (alcohol* near/2 (drink* or intoxicat* or use* or abus* or misus* or risk* or consum* or withdraw* or detox* or treat* or therap* or excess* or reduc* or cessation or intervention*))) #4 #3 OR #2 #5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR

(*Continued*)

		meta-analysis OR systematic review* OR meta-analys*) #6 #5 AND #4 AND #1
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	Date of search to be provided at review stage	Condition: fatty liver Phases: 2,3,4
ClinicalTrials.gov	Date of search to be provided at review stage	Fatty Liver, Nonalcoholic | Phase 2, 3, 4
European Medical Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	Date of search to be provided at the review stage	"Fatty liver"; random

Footnote: This is a common search strategy that will be used for this review and nutritional supplementation review (Gurusamy 2018b).

Appendix 2. Sample size calculation

The five-year mortality in people with non-alcohol related fatty liver disease is about 20% (Adams 2005). The required information size based on a control group proportion of 20%, a relative risk reduction of 20% in the experimental group, type I error of 5%, and type II error of 20% is 2894 participants. Network analyses are more prone to the risk of random errors than direct comparisons (Del Re 2013). Accordingly, a greater sample size is required in indirect comparisons than direct comparisons (Thorlund 2012). The power and precision in indirect comparisons depends upon various factors, such as the number of participants included under each comparison and the heterogeneity between the trials (Thorlund 2012). If there is no heterogeneity across the trials, the sample size in indirect comparisons would be equivalent to the sample size in direct comparisons. The effective indirect sample size can be calculated using the number of participants included in each direct comparison (Thorlund 2012). For example, a sample size of 2500 participants in the direct comparison A versus C (n_{AC}) and a sample size of 7500 participants in the direct comparison B versus C (n_{BC}) results in an effective indirect sample size of 1876 participants. However, in the presence of heterogeneity within the comparisons, the sample size required is higher. In the above scenario, for an I^2 statistic for each of the comparisons A versus C (I_{AC}^2) and B versus C (I_{BC}^2) of 25%, the effective indirect sample size is 1407 participants. For an I^2 statistic for each of the comparisons A versus C and B versus C of 50%, the effective indirect sample size is 938 participants (Thorlund 2012). If there are only three groups and the sample size in the trials is more than the required information size, we will calculate the effective indirect sample size using the following generic formula (Thorlund 2012):
$((n_{AC} \times (1 - I_{AC}^2)) \times (n_{BC} \times (1 - I_{BC}^2))/((n_{AC} \times (1 - I_{AC}^2)) + (n_{BC} \times (1 - I_{BC}^2))$.
Currently, there is no method to calculate the effective indirect sample size for a network analysis involving more than three intervention groups.

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: KG

Designing the protocol: KG

Co-ordinating the protocol: KG

Designing search strategies: KG

Writing the protocol: KG

Providing general advice on the protocol: AM, ET

Securing funding for the protocol: KG

Performing previous work that was the foundation of the current study: not applicable

DECLARATIONS OF INTEREST

None known for any of the authors.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.

Payment for writing reviews, writing equipment, software

NOTES

The methods section of this protocol is based on a standard Cochrane Hepato-Biliary Group template, incorporating advice from the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).