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Modified dietary fat intake for treatment of gallstone disease (Protocol)

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[Intervention Protocol]

Modified dietary fat intake for treatment of gallstone disease

Angela M Madden[1], Daksha Trivedi[2], Nigel C Smeeton[2], Alison Culkin[3]

[1]Biological & Environmental Sciences, University of Hertfordshire, Hatfield, UK. [2]Centre for Research in Primary and Community Care, University of Hertfordshire, Hatfield, UK. [3]Nutrition & Dietetic Department, St Mark's Hospital, Harrow, UK

Contact address: Angela M Madden, Biological & Environmental Sciences, University of Hertfordshire, College Lane, Hatfield, Hertfordshire, AL10 9AB, UK. a.madden@herts.ac.uk.

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ABSTRACT

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

To assess the benefits and harms of modifying dietary fat intake in the treatment of gallstone disease.

BACKGROUND

Gallstone disease, also known as cholelithiasis, is characterised as hard deposits or stones in the gallbladder and biliary tract. A normally functioning gallbladder stores bile and releases it into the small intestine when it is needed for digestion. Gallstones can develop if the bile contains too much cholesterol or bilirubin, if the gallbladder is dysfunctional, or if the release of bile is impaired. The type of gallstone is defined by its composition and can be divided into two main groups, those that are cholesterol-rich, which comprise approximately 70% of patients from Western countries, and those that are composed predominantly of bile pigments (Venneman 2010).

Recognised risk factors for the disease include female sex, hereditary predisposition, increasing age and body mass index (BMI), rapid weight loss, diabetes, and gastrointestinal and biliary factors, including infection. Prevalence of cholesterol gallstones is generally considered to be increasing as a consequence of nutritional and lifestyle changes, ageing populations, the increasing global prevalence of obesity, and improved diagnostic capabilities (Stinton 2010; Stokes 2014a; Aune 2016).

Gallstones can be diagnosed on the basis of medical history, clinical findings, and imaging, the most appropriate method of which is abdominal ultrasound imaging, which is supported by high quality evidence (EASL 2016).

Surgery for gallstones is associated with a mortality of less than 2% of all surgical deaths (Scollay 2011). The burden of morbidity, and direct and indirect costs are high. For example, in the USA, the estimated cost of treating gallstone disease is approximately USD 6.2 billion annually (Stinton 2010; Stokes 2014a).

Description of the condition

People who develop cholelithiasis may have no symptoms at all, while others may experience severe abdominal pain (biliary colic), nausea, and vomiting. It is estimated that approximately 10% of the population with asymptomatic gallstones will develop symptoms or require treatment within five years (Halldestam 2004). These include cholecystitis, and less commonly, obstructive jaundice, cholangitis, acute pancreatitis, and gangrene of the gallbladder.

Description of the intervention

Symptomatic gallstone disease is often treated by surgically removing the gallbladder (cholecystectomy), most commonly undertaken laparoscopically (EASL 2016; Keus 2006). While this may be common practice, medical management can also be a first line treatment and can include dissolving the gallstones with drug therapy (for example, with ursodeoxycholic acid (May 1993)).

However, traditionally, restricting dietary fat intake was used to reduce the pain associated with gallbladder contractions, rather than dissolving the gallstones. A survey of dietary practice in the UK published 20 years ago indicated that people were regularly advised to restrict fat to manage their gallstone disease, but at that time, there was limited empirical evidence to justify this approach (Madden 1992). Mogadam 1984 also reported that dietary fat restriction was a frequent method of management, but contested the therapeutic relevance of this form of dietary management.

Currently, authoritative sources of information for people with gallstone disease advise adherence to low fat, low cholesterol diets, or both (British Liver Trust 2011; Radio 4 2012; Patient 2014; BUPA 2015). This suggests that a dietary intervention is still current treatment for this disease, even though the rationale appears to be uncertain. A preliminary review of the literature indicates that there is no published evidence of the benefits of a low fat diet compared with standard diet. However, with the increasing prevalence of obesity, there is evidence that people with obesity, who are advised to follow weight-reducing diets that incorporate a very low fat diet, may be more likely to develop gallstones (Festi 2000), and that diets higher in fat may reduce gallstone risk in adults losing weight (Stokes 2014b). We do not anticipate that specific populations would experience different outcomes from interventions.

How the intervention might work

The rationale for restricting or modifying dietary fat in the treatment of gallstone disease has two putative mechanisms.

First, as dietary fat is a potent stimulator of gallbladder contraction, dietary fat may provoke or exacerbate post-prandial pain, and therefore, hypothetically, restricting dietary fat might reduce pain. However, the gallbladder also contracts spontaneously (Behar 1989), and in response to an intake of mixed meals, protein (Hopman 1985), or cephalic stimulation (Hopman 1987). Furthermore, if restricting dietary fat does lead to a reduction in gallbladder contractions and emptying, it may also increase the risk of gallstone deposition, as lithogenic bile would be retained longer in the gallbladder. thus potentially exacerbating the problems.

Second, reducing total dietary fat, and particularly saturated fat, leads to a reduction in plasma cholesterol. Lower plasma cholesterol levels may be accompanied by a parallel reduction in biliary cholesterol concentration, which would reduce the precipitation of cholesterol in the bile, and decrease the risk of forming cholesterol-rich gallstones (Mendez-Sanchez 2007). This potential mechanism is complicated by the fact that circulating cholesterol levels are more influenced by endogenous cholesterol synthesis than by the intake of dietary cholesterol per se (Lecerf 2011). If this mechanism provides a rationale for the potential treatment of cholesterol-rich stones, it is unlikely to be relevant to the management of stones composed predominantly of pigment.

Why it is important to do this review

Evidence for the role of dietary intervention in the primary prevention of gallbladder stones in adults is currently under review (Stokes 2014a). Dietary advice to restrict or modify fat intake, which is currently promoted as treatment for people with gallstones, does not appear to be based on rationalised evidence. While there are general health benefits associated with avoiding excessive dietary fat, i.e. reduced risk of obesity and cardiovascular disease, specific benefits for the treatment of gallstone disease need clarification (NICE 2014). First, it is important to determine if there are benefits from modifying fat intake, or detrimental effects from reduced gallbladder emptying. Second, it would be informative to quantify the amount of fat reduction needed, so that tailored advice could be given, in particular to the minority of patients with gallstone disease who are underweight and potentially at risk of malnutrition.

This review will systematically examine the evidence for the dietary management of gallstone disease, clarify the therapeutic benefits and potential risks of dietary interventions as alternatives to, or interim measures while waiting for surgical intervention, and identify the need for future research.

OBJECTIVES

To assess the benefits and harms of modifying dietary fat intake in the treatment of gallstone disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials for assessments of benefits and harms.

We will only include non-randomised studies or quasi-randomised studies for assessment of harms. We will not search specifically for such studies, and are aware that this is a limitation of our review.

Types of participants

We will include trials in which the participants have gallstone disease, were diagnosed using ultrasound, and are receiving a dietary intervention, which may or may not have the primary purpose of treating gallstones.
Participants can be male or female, of any age, or ethnic origin.
We will exclude trials with participants who have been diagnosed with another condition that may compromise dietary fat tolerance, e.g. cholestatic liver disease, short bowel, intestinal failure, or pancreatic insufficiency.

Types of interventions

We will include trials in which the intervention examines the beneficial or harmful effects, or both, of any type of modification of dietary fat intake compared with standard care (no specific additional or alternative intervention), or compared with any other type of dietary modification, providing that fat intake can be quantified in both study groups, i.e. as either grams of fat per day or per test meal, or expressed as percentage energy. We will conduct these analyses separately. The intervention might include, for example, restriction of total fat intake, modification of cholesterol intake, long chain fatty acid intake, saturated fat intake, plants sterols and stanols, and fat from specific sources, such as dairy fat or animal fat. We will also include trials in which the intervention examines the beneficial or harmful effects of dietary components that have an effect on fat absorption or reabsorption of bile acids, e.g. psyllium or soluble fibre (Ganji 1994; Theuwissen 2008). In some cases, we may identify trials that compare modified dietary fat against another format of modified dietary fat, or against another dietary intervention that may not have a modified dietary fat component, for example, modified dietary fat versus vitamin C intake, or adjustments to fibre intake.
We will include trials with any level of dietary fat modification, providing that it differs from the comparison group.
Some trials may have different modes of delivery to the gastrointestinal tract, e.g. oral or enteral nutrition, both of which we will include. However, we will exclude trials where the intervention or comparison are exclusively parenteral, i.e. include no oral or enteral intake.
We will include trials that test the effects of the frequency and timing of dietary fat intake.
We will also include trials that have three or more dietary interventions, as long as one of the groups contains a form of dietary modification as described above, and we will take account of additional groups during analysis, as described below.
We will include trials that include a co-intervention, e.g. drugs, if the trial groups have received the same proportion of drug intervention with a dietary modification, or if there are separate groups in the trial in which there have been no drug co-interventions.

Types of outcome measures

Primary outcomes

- All-cause mortality and gallstone morbidity, i.e. documented cholecystitis, gallstone pancreatitis, biliary colic, obstructive jaundice, and cholangitis.
- Dissolution or reduction in size of gallstones.
- Serious adverse events. Depending on the availability of data, we will attempt to classify adverse events as serious or non-serious. We will define a serious adverse event according to the *International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice,* as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, or any medical event that might jeopardise the patient, or requires an intervention to prevent it (ICH-GCP 1997). All other adverse events (that is, any medical occurrence, not necessarily having a causal relationship with the treatment, but leading to a dose reduction or discontinuation of the treatment) are considered non-serious.
- Health-related quality of life, assessed using validated tests.

Secondary outcomes

- Number of patients admitted to hospital.
- Number of patients subjected to a surgical intervention.
- Number of people with non-serious adverse events.

Search methods for identification of studies

Electronic searches

We will identify studies by searching the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded via Web of Science (Royle 2003). We have provided preliminary search strategies with the expected time spans of the searches in Appendix 1. We will include reports of trials in languages other than English, providing we can obtain a reliable translation.

Searching other resources

We will identify other relevant studies by searching reference lists of identified trials and conference proceedings.
We will also search on-line trial registries, such as ClinicalTrial.gov (clinicaltrials.gov/), European Medicines Agency (EMA; www.ema.europa.eu/ema/), WHO International Clinical Trial

Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA; www.fda.gov), and pharmaceutical company sources, for ongoing or unpublished trials.

Data collection and analysis

We will perform the review following Cochrane recommendations (Higgins 2011), and the Cochrane Hepato-Biliary Group Module (Gluud 2017). We will use Review Manager 5 for the analyses (RevMan 5 2014).

Selection of studies

Two review authors will independently review the titles and abstracts of studies identified by the electronic searches and agree on potential publications. We will retrieve the full text of all apparently relevant studies. Two review authors will independently assess the full text of potential studies for inclusion in the review according to the pre-specified criteria. We will resolve differences in opinion by discussion. In the event that we cannot resolve differences, we will ask a third author to provide an opinion. We will keep a record of all included and excluded studies that are selected from the title review.

Data extraction and management

We will adapt the Cochrane Hepato-Biliary Group data collection form and pilot this on one study (CHBG 2014). We will then use the adapted form to record study characteristics from the included studies on design, interventions, participants, and outcomes as described in the Criteria for considering studies for this review section above. Two review authors will independently extract the data. We will resolve differences in extracted results by discussion, and in the event of no agreement, we will ask a third author to provide an opinion.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in each of the included studies. We will use Cochrane criteria for judging risk of bias in randomised studies (Higgins 2011). The Cochrane 'risk of bias' tool criteria assess strictly 'random' components as 'low risk' and 'non-random' components as 'high risk' of bias. We will use the following definitions in our assessment (Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012; Savovic 2012a; Schulz 1995; Wood 2008).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved 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 trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random. Such studies will be included only for assessments of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. Such studies will be included only for assessments of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinded outcome assessment

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

assessment, but likely that the blinding could have been broken, and the outcome measurement is 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. Sufficient methods, such as multiple imputation, have been employed 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 clinically relevant outcomes (all-cause mortality and gallstone morbidity, dissolution or reduction in size of gallstones, and serious adverse events). If we have access to the original trial protocol, the outcomes selected would be those called for in that protocol. We will use information from trial registries such as www.clinicaltrials.gov only if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: it is unclear whether all clinically relevant and reasonably expected outcomes were reported.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appears to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conduct, or results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias, as no information on clinical trial support or sponsorship is provided.
- High risk of bias: the trial is sponsored by the industry, or has received other kinds of for-profit support.

Other risk of bias

The following will be considered: baseline imbalance; deviation from study protocol; pre-randomisation administration of the intervention or inappropriate administration; sparse data bias, academic bias, early stopping for perceived benefit without an a priori plan (Greenland 2016).

- Low risk of bias: the trial appears to be free of other sources of bias.
- Uncertain risk of bias: there is insufficient information to assess whether other sources of bias are present.
- High risk of bias: it is likely that potential sources of bias related to the specific trial design used, or other bias risks, are present.

We will consider trials to be at low risk of bias if assessed at 'low risk of bias' in all the above domains; in all other cases, we will consider the trials at high risk of bias.

Measures of treatment effect

We will analyse outcomes measured as continuous data (such as patient reported data using a visual analogue scale) using means and mean differences with their corresponding standard deviations and standard errors, and reported with 95% and Trial Sequential Analysis-adjusted confidence intervals (CIs). We will analyse dichotomous data using odds ratios or risk ratios, and reported with 95% and Trial Sequential Analysis-adjusted CIs. If trials have multiple intervention groups, we will try to combine categories to forms two groups (Higgins 2011).

Unit of analysis issues

The trial participants in a randomised clinical trial.

Dealing with missing data

We will try to find data on all participants who were randomised, so that we can undertake intention-to-treat analyses, which will include all participants, regardless of adherence or complete follow-up. In cases where outcome data for excluded participants have not been published, we will contact the authors of the trial and request their original data. We will gather information on non-completing participants, including the time and reason for drop-out, as described by the trial authors, and record this on the information extraction form. In addition, we will perform 'worst-best case scenario' and 'best-worst case scenario' analyses for participants lost to follow-up (Gluud 2017).

Assessment of heterogeneity

We will assess the presence of statistical heterogeneity using the Chi^2 test. Where the P value is less than 0.1, we will assume there is significant heterogeneity, and quantify heterogeneity using the I^2 statistic (DerSimonian 1986; Higgins 2002). If intervention studies are combined, errors may arise during the assessment of heterogeneity due to differences in units of analysis. To address this, we will use a fixed-effect analysis of comparisons within a trial and then a random-effect analysis between trials.

Assessment of reporting biases

We will develop a funnel plot using Review Manager 5 to evaluate bias by demonstrating the treatment effect against trial size (RevMan 5 2014).

Data synthesis

Meta-analysis

We intend to undertake meta-analysis and present the findings according to Cochrane recommendations (Higgins 2011). We will combine data from trials with similar populations, interventions, comparisons, and outcomes. If different scales are used to measure the same outcome, we will present the standardised mean difference. We will calculate P values for all comparisons where this is possible. We will undertake intention-to-treat analyses wherever possible, so that all randomised patients are included. Where this is not possible, we will carry out an analysis of available participant cases.

If we include a small number of trials, or if the number of participants is small, we will use the Mantel-Haenszel method for pooling dichotomous data, as this assumes a fixed-effect meta-analysis, and is considered an appropriate method (Mantel 1959; Higgins 2011). For continuous data, we will use standardised or mean differences to pool results. If there is no heterogeneity between study findings, we will synthesise and analyse data using a fixed-effect model meta-analysis (Demets 1987). If this is not possible, we will use the random-effects model (DerSimonian 1986).

Trial Sequential Analysis

Where possible, we will examine apparently significant beneficial and harmful intervention effects and neutral effects with Trial Sequential Analysis (Thorlund 2011; TSA 2016), in order to evaluate if these apparent effects could be caused by random error or 'play of chance' (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010).

We will perform Trial Sequential Analysis (TSA) on the data, primarily from the trials with a low risk of bias (Brok 2008; Wetterslev 2008). However, if we do not identify any trials with low risk of bias, we will discuss which trials to include. We will analyse the outcomes using TSA, regardless of the statistical significance of the results. The pooled estimate of the control event proportions of the trials with low risk of bias will be used as the control event proportion in the TSA. We will use the pooled estimate of the intervention effect using the trials with low risk of bias, and also perform a sensitivity analysis, using an intervention effect of a 20% risk ratio reduction. The unit of the intervention effect for all dichotomous data will be risk ratio reduction.

For each TSA performed, we will calculate a diversity-adjusted required information size, based on the intervention effect suggested by trials with a low risk of bias and an intervention effect of 20% risk ratio reduction, a type I error risk of 2.0% and a type II error risk of 10% (Wetterslev 2009). The diversity adjustment will be performed using the observed diversity adjustment factor $1/(1 - D^2)$, the heterogeneity estimated by D^2 among all trials, and with an assumed final diversity of 50% (Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

If there is apparent significant clinical heterogeneity, we will perform subgroup analyses. These will include trials at low risk of bias compared to trials at high risk of bias, trials that included adults compared to children (0 to 18 years); male compared to female; gallstone type; acute versus chronic disease; body weight; body mass index category, presence of diabetes compared to normoglycaemia (Stinton 2010; Stokes 2014a; Aune 2016). If there is apparent significant clinical heterogeneity between the trials, we will specifically examine the degree of heterogeneity we observe in the results with the I^2 statistic , using the guideline that an I^2 statistic value of 50% or more indicates a substantial level of heterogeneity (Higgins 2002; Higgins 2003).

Sensitivity analysis

If we identify a sufficient number of randomised trials, we will perform sensitivity analyses to examine the impact of the following factors on effect size:

- size of trials (e.g. large trials).
- trials identified using the following filters: diagnostic criteria; language of publication; source of funding (industry compared to other).
- duration of intervention (e.g. impact of short compared to long interventions).

'Summary of findings' tables

We will use the GRADE approach to evaluate the quality of the evidence for outcomes reported in the review by considering the within-study risk of bias (methodological quality), indirectness of evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimate (wide conference intervals as evaluated with our Trial Sequential Analyses; Jakobsen 2014), and risk of publication bias (GRADEpro GDT; Meader 2014). We will define the evidence as 'high', 'moderate', 'low', or 'very low' certainty. These levels are defined as follows.

- High certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.
- Moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.

- Low certainty: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different is high.
- Very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

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Peer Reviewers: Joshua Feinberg, Denmark; Luit Penninga, Denmark.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date of search	(diet* AND fat* AND (restrict* OR modif*)) AND (cholelithiasis OR gallstone* OR 'gall stone*' OR gallstone*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor Nutrition Therapy explode all trees #2 MeSH descriptor Dietary Fats explode all trees #3 MeSH descriptor Diet, Fat-Restricted explode all trees #4 diet* AND fat* AND (restrict* OR modif*) #5 (#1 OR #2 OR #3 OR #4) #6 MeSH descriptor Cholelithiasis explode all trees #7 cholelithiasis OR gallstone* OR gall stone* OR gallstone* #8 (#6 OR #7) #9 (#5 AND #8)
MEDLINE Ovid	1946 to the date of search	1. exp Nutrition Therapy/ 2. exp Dietary Fats/ 3. exp Diet, Fat-Restricted/ 4. (diet* and fat* and (restrict* or modif*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 5. 1 or 2 or 3 or 4 6. exp Cholelithiasis/ 7. (cholelithiasis or gallstone* or gall stone* or gall-stone*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 8. 6 or 7 9. 5 and 8 10. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 11. 9 and 10
Embase Ovid	1974 to the date of search	1. exp diet therapy/ 2. exp fat intake/ 3. (diet* and fat* and (restrict* or modif*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

(*Continued*)

		4. 1 or 2 or 3 5. exp cholelithiasis/ 6. (cholelithiasis or gallstone* or gall stone* or gall-stone*) .mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 7. 5 or 6 8. 4 and 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 8 and 9
Science Citation Index Expanded (Web of Science)	1900 to the date of search	# 5 #4 AND #3 # 4 TS=(random* or blind* or placebo* or meta-analys*) # 3 #2 AND #1 # 2 TS=(cholelithiasis or gallstone* or gall stone* or gall-stone*) # 1 TS=(diet* and fat* and (restrict* or modif*))

CONTRIBUTIONS OF AUTHORS

All authors contributed to the preparation of this review protocol and approved the final version. AM and AC contributed subject expertise; AM and DT contributed systematic review expertise; NS contributed statistical expertise.

DECLARATIONS OF INTEREST

AM: none known.

DT is an editor with the Cochrane Injuries Group.

NS: none known.

AC: none known.

SOURCES OF SUPPORT

Internal sources

- University of Hertfordshire, UK.

Access to electronic resources including peer reviewed journals.

External sources

- No sources of support supplied