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Modified dietary fat intake for treatment of gallstone disease in people of any age (Review)

Madden AM, Smeeton NC, Culkin A, Trivedi D

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Modified dietary fat intake for treatment of gallstone disease in people of any age.
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[Intervention Review]

Modified dietary fat intake for treatment of gallstone disease in people of any age

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ABSTRACT

Background

The prevalence of gallstones varies between less than 1% and 64% in different populations and is thought to be increasing in response to changes in nutritional intake and increasing obesity. Some people with gallstones have no symptoms but approximately 2% to 4% develop them each year, predominantly including severe abdominal pain. People who experience symptoms have a greater risk of developing complications. The main treatment for symptomatic gallstones is cholecystectomy. Traditionally, a low-fat diet has also been advised to manage gallstone symptoms, but there is uncertainty over the evidence to support this.

Objectives

To evaluate the benefits and harms of modified dietary fat intake in the treatment of gallstone disease in people of any age.

Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE ALL Ovid, Embase Ovid, and three other databases to 17 February 2023 to identify randomised clinical trials in people with gallstones. We also searched online trial registries and pharmaceutical company sources, for ongoing or unpublished trials to March 2023.

Selection criteria

We included randomised clinical trials (irrespective of language, blinding, or status) in people with gallstones diagnosed using ultrasonography or conclusive imaging methods. We excluded participants diagnosed with another condition that may compromise dietary fat tolerance. We excluded trials where data from participants with gallstones were not reported separately from data from participants who did not have gallstones. We included trials that investigated other interventions (e.g. trials of drugs or other dietary (non-fat) components) providing that the trial groups had received the same proportion of drug or other dietary (non-fat) components in the intervention.

Data collection and analysis

We intended to undertake meta-analysis and present the findings according to Cochrane recommendations. However, as we identified only five trials, with data unsuitable and insufficient for analyses, we described the data narratively.

Main results

We included five trials but only one randomised clinical trial (69 adults), published in 1986, reported outcomes of interest to the review.

The trial had four dietary intervention groups, three of which were relevant to this review. We assessed the trial at high risk of bias. The dietary fat modifications included a modified cholesterol intake and medium-chain triglyceride supplementation. The control treatment was a standard diet. The trial did not report on any of the primary outcomes in this review (i.e. all-cause mortality, serious adverse events, and health-related quality of life). The trial reported on gallstone dissolution, one of our secondary outcomes. We were unable to apply the GRADE approach to determine certainty of evidence because the included trial did not provide data that could be used to generate an estimate of the effect on this or any other outcome. The trial expressed its finding as "no significant effect of a low-cholesterol diet in the presence of ursodeoxycholic acid on gallstone dissolution." There were no serious adverse events reported.

The included trial reported that they received no funding that could bias the trial results through conflicts of interest.

We found no ongoing trials.

Authors' conclusions

The evidence about the effects of modifying dietary fat on gallstone disease versus standard diet is scant. We lack results from high-quality randomised clinical trials which investigate the effects of modification of dietary fat and other nutrient intakes with adequate follow-up. There is a need for well-designed trials that should include important clinical outcomes such as mortality, quality of life, impact on dissolution of gallstones, hospital admissions, surgical intervention, and adverse events.

PLAIN LANGUAGE SUMMARY

Is changing dietary fat intake beneficial or harmful for people with gallstones?

Key message

– Evidence about the effects of dietary fat intake on the wellbeing of people with gallstones is uncertain.

What are gallstones?

Gallstones, also known as cholelithiasis, are deposits from digestive fluid which consist of solidified substances such as cholesterol and bile pigments that are found in bile (a fluid that breaks down fats and is made and released by the liver and stored in the gallbladder). Cholesterol (a fat-like substance) circulates in the blood and all the body's cells contain cholesterol. Too much cholesterol can cause numerous health problems. The number of people with gallstones is generally increasing because of nutritional and lifestyle changes, ageing populations, increasing levels of obesity, and improvements in diagnosis.

What did we want to find out?

We wanted to find out if changing dietary fat intake is beneficial or harmful for people with gallstones. We were interested in the effects on deaths, serious side effects, health-related quality of life (a measure of a person's satisfaction with their life and health), dissolving or reducing the size of the gallstones, or non-serious side effects.

What did we do?

We searched medical databases for clinical trials of people with gallstones who received a dietary intervention that aimed to treat gallstones.

What did we find?

We identified five trials, but only one trial with 69 participants provided some data for this review. The trial was carried out in the USA and was published in 1986. Thirty-seven (54%) people were women and all were adults. The trial randomly assigned 69 people to a modified diet including a low-cholesterol intake diet or a modified diet with additional medium-chain triglyceride (a type of fat that may be easier to absorb without bile), and compared them to a standard diet.

Key results

There was not enough evidence to state whether modifying dietary fat has beneficial, harmful, or neutral effects on outcomes of people with gallstones. The one trial that reported data did not investigate key concerns including whether modifying dietary fat influenced people's symptoms after eating, their health-related quality of life, their chance of having gallbladder inflammation, or requiring surgery to remove their gallbladder.

We found no ongoing trials.

Funding

The one trial that reported data received no funding that could bias the trial results through conflicts of interest.

What are the limitations of the evidence?

Our confidence in the evidence was very low because we were concerned about the methods used in the trial (for example, how the participants were allocated to their treatments, the trial did not report data about everything that we were interested in, there was no information about who delivered the dietary intervention). The results of further research could differ from the results of this review.

How up to date is this evidence?

The evidence is current to 17 February 2023.

Summary of findings 1. Modified dietary fat intake for treatment of gallstone disease in people of any age

Patient or population: participants with gallstone disease (cholesterol, pigment, or mixed)
Setting: any setting
Intervention: any type or level of modification of dietary fat intake
Comparison: standard care

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	№ of participants (studies) *	Certainty of the evidence (GRADE)	Comments
	Risk with standard care (i.e. no specific additional or alternative intervention), or versus any other type of dietary modification excluding dietary fat	Risk with any type or level of modification of dietary fat intake				
All-cause mortality	—	—	—	—	—	Not reported
Serious adverse events at longest follow-up	—	—	—	—	—	Not reported
Health-related quality of life	—	—	—	—	—	Not reported

***The risk in the intervention group** (and its 95% confidence interval) 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 certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] We found no trials that reported on any of the planned primary outcomes in our review protocol.

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 are the form predominantly found in people with 'Western' lifestyles; and those that are composed predominantly of bile pigments (Jones 2023a).

Recognised risk factors for the disease include female sex, hereditary predisposition, increasing age, increasing body mass index, rapid weight loss, diabetes, and gastrointestinal and biliary factors, including infection. The prevalence of gallstones varies with the sex, age, ethnicity, socioeconomic status, and health status, including metabolic disease, of the population studied, and the diagnostic criteria used; recent population studies indicate a prevalence between 5% and 13.9% (Colvin 2022; Unalp-Arida 2023). People with haemolytic anaemia are at greater risk of pigment-rich stones (Jones 2023a). The 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 (Aune 2016; Dupont 2022; Stinton 2010).

Gallstones can be diagnosed based on medical history, clinical findings, and imaging. The most appropriate imaging methods are abdominal ultrasound imaging (supported by high-quality evidence) and, if ultrasound results are inconclusive, magnetic resonance imaging (EASL 2016).

Currently, cholecystectomy, either via a laparoscopic or open surgery approach, is the standard treatment for symptomatic cholecystolithiasis (EASL 2016; Keus 2006). It is estimated that more than 1.2 million people undergo cholecystectomy each year in the USA (Jones 2023b).

Description of the condition

Some people who develop gallstone disease may have no symptoms at all, while others may experience severe abdominal pain (biliary colic), nausea, and vomiting. It is estimated that 2% to 4% of people with gallstones develop symptoms each year (Gurusamy 2014). People with gallstone symptoms have a risk of between 1% and 3% of developing complications annually (Brazzelli 2014), which is higher than the annual complication risk of those who are asymptomatic (Brazzelli 2014; Festi 2010). The risk of complications is also influenced by the location of the gallstones, as those lodged in the common bile duct carry a higher risk. Complications include cholecystitis, and, less commonly, obstructive jaundice, cholangitis, acute pancreatitis, and gangrene of the gallbladder. The presence of gallstones is also associated with a higher risk of gallbladder cancer (Sharma 2017).

Description of the intervention

Symptomatic gallstone disease is often treated by cholecystectomy (i.e. gallbladder removal surgery, undertaken laparoscopically or via open surgery) (EASL 2016; Keus 2006). While this may be common practice, medical management can also be a first-line treatment. This can include percutaneous extraction of gallstones in people who are not suitable for surgery (Latif 2023).

Restricting dietary fat intake was traditionally used to reduce the pain associated with gallbladder contractions. One survey of dietary practices in the UK 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 and colleagues also reported that dietary fat restriction was a frequent method of management but contested the therapeutic relevance of this form of dietary management (Mogadam 1984).

Currently, sources of information for people with gallstone disease advise adherence to low-fat or low-cholesterol diets, or both (British Liver Trust 2018; Healthline 2018; MyHealth.Alberta.ca 2022; Patient 2020). This suggests that dietary intervention is still considered a treatment for this disease, even though the rationale appears to be uncertain. We consider 'treatment' to mean something that is designed to play a role in the management of the condition as part of clinical nutrition practice, rather than to prevent gallstones from forming. A preliminary review of the literature indicated that there was no published evidence of the benefits of a low-fat diet compared with a standard diet. 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 2014). It should be noted that specific populations might experience different outcomes from the interventions, for example, due to differences associated with ethnicity, socioeconomic status, or the presence of comorbidities such as metabolic disease.

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 postprandial pain. 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 problem. This mechanism is relevant for gallstones composed of cholesterol and pigment.

Second, reducing total dietary fat, 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). This mechanism is relevant to the management of stones composed predominantly of cholesterol.

Why it is important to do this review

Dietary advice to restrict or modify fat intake in 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), current UK guidelines indicate that specific benefits of a modified diet for the treatment of gallstone disease need clarification (NICE 2014). First, it is still important to determine if there are benefits from modified 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 people with gallstone disease who are underweight and potentially at risk of malnutrition. We could find no meta-analyses or systematic reviews assessing either the benefit or harm of modifying fat intake or quantifying fat reduction.

This review was planned to systematically examine the evidence for the dietary management of gallstone disease, clarify the therapeutic benefits and potential risks of dietary interventions, and identify the need for future research (Madden 2017; Madden 2021).

OBJECTIVES

To evaluate the benefits and harms of modified dietary fat intake in the treatment of gallstone disease in people of any age.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials assessing benefits and harms of any type of modification of dietary fat intake versus standard care (i.e. no specific additional or alternative intervention), or versus any other type of dietary modification. Cluster-randomised clinical trials and cross-over randomised clinical trials were eligible. We planned to use only the data from the first trial period of the cross-over design to avoid residual effects from the intervention (Higgins 2021a; Higgins 2021b). We excluded quasi-randomised clinical studies (i.e. where a quasi-random method of allocation was used, such as alternation, date of birth, or case record number), or observational studies unless they reported harms. Observational studies were identified from items identified by the searches but excluded at screening or full-text review.

Types of participants

Inclusion criteria

We considered for inclusion trials of participants with gallstone disease (cholesterol, pigment, or mixed) diagnosed using ultrasound or conclusive imaging methods, who received a dietary intervention that might have had the primary or adjunctive purpose of treating gallstones.

Participants included males and females of any age or ethnic origin.

Exclusion criteria

We excluded participants who had been diagnosed with another condition that could have compromised dietary fat tolerance (e.g. cholestatic liver disease, short bowel, intestinal failure, or pancreatic insufficiency).

We excluded groups of participants that included people with and without gallstones, if these could not be analysed separately.

Types of interventions

Experimental intervention

The experimental intervention was any type or level of modification of dietary fat intake, providing that it differed from the comparison group.

We considered including experimental interventions with restriction of total fat intake, modification of cholesterol intake, and supplementation with medium-chain triglycerides. We planned to evaluate quantitative changes in fat intake by assessing either grams of dietary fat intake per day or per test meal, or the percentage energy from dietary fat. We planned to include experimental interventions with modification of long-chain fatty acid intake, saturated fat intake, plant sterols and stanols, and fat from specific sources (such as dairy fat or animal fat); however, no such interventions were included in records identified during the search.

We considered for inclusion trials with oral delivery of diet and different modes of delivery to the gastrointestinal tract (e.g. oral or enteral nutrition). However, we excluded trials where the intervention or comparison was exclusively parenteral (i.e. did not include oral or enteral intake).

We considered the inclusion of trials that tested the effects of the frequency and timing of dietary fat intake, but no such interventions were included in records identified during the search.

We also considered the inclusion of trials that had three or more dietary interventions, as long as one of the groups contained a form of dietary modification as described above, and we took account of additional groups during the analysis, as described below (Unit of analysis issues).

We considered for inclusion trials that had a co-intervention, such as drugs or other dietary (non-fat) components (e.g. psyllium or soluble fibre (Ganji 1994; Theuwissen 2008)), providing that all trial groups had received the same proportion of drug or other dietary (non-fat) components in the intervention.

Control intervention (comparison group)

The comparison group was standard care (i.e. no specific additional or alternative intervention), or any other type of dietary modification excluding dietary fat, providing that fat intake could be quantified in both trial groups (i.e. quantified as grams of fat per day or per test meal, or expressed as percentage energy). We analysed trials where the control intervention was standard care (no additional or alternative intervention) separately from those where the control intervention was any other type of dietary modification excluding dietary fat.

Types of outcome measures

We included data from trials that reported at least one of the defined primary and secondary outcomes of the systematic review. We planned to collect data with their ranges of follow-up and to assess all outcomes at the longest follow-up.

Primary outcomes

- All-cause mortality.
- Proportion of participants with serious adverse events at longest follow-up. Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. We recorded how serious adverse events were assessed in each study according to Good Clinical Practice (GCP). We defined a serious adverse event according to the *International Conference on Harmonization (ICH) Guidelines for GCP,* 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" (ICH-GCP 2016). This reflects the description used in another Cochrane review protocol (Markotic 2020). We intended to specifically report on hepatobiliary conditions including cholecystitis, pancreatitis, cholangitis, obstructive jaundice, and gallbladder cancer. We considered any other adverse events to be non-serious (i.e. any medical occurrence, not necessarily having a causal relationship with the treatment, but leading to a dose reduction or discontinuation of the treatment).
- Health-related quality of life, assessed using validated tests (e.g. the five-dimension EuroQol (EQ-5D) scale (EuroQol Group 1990), or the 36-item Short Form (SF-36) tool (Garratt 1993)).

Secondary outcomes

- Proportion of participants without dissolution or reduction in size of gallstones.
- Proportion of participants with any other adverse events not considered as serious as above.

Search methods for identification of studies

Electronic searches

We identified trials by searching the Cochrane Hepato-Biliary Group Controlled Trials Register which was searched internally by the Cochrane Hepato-Biliary Group Information Specialist via the Cochrane Register of Studies Web. We also searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 2) in the Cochrane Library, MEDLINE ALL Ovid, Embase Ovid, LILACS (Latin American and Caribbean Health Science Information database; Virtual Health Library Regional Portal), Science Citation Index Expanded, and Conference Proceedings Citation Index – Science. The latter two were searched simultaneously through Web of Science. The electronic searches were performed on 17 February 2023.

Appendix 1 gives the search strategies with the date range of the searches.

Searching other resources

Two review authors (AMM and AC) searched reference lists of identified trials, conference proceedings, and documents that cited our protocol (Madden 2017; Madden 2021).

We searched the online trial registries ClinicalTrials.gov (clinicaltrials.gov/), European Union Clinical Trials Registry (EU CTR; www.clinicaltrialsregister.eu/ctr-search/search), World Health Organization International Clinical Trial Registry Platform (WHO ICTRP; trialsearch.who.int/), and pharmaceutical company sources, for ongoing or unpublished trials. We searched for grey literature in the System for Information on Grey Literature in Europe OpenGrey (www.opengrey.eu) and its archive (easy.dans.knaw.nl/ui/home).

Appendix 1 gives the search terms used for searching other resources. Searches were performed in March 2023.

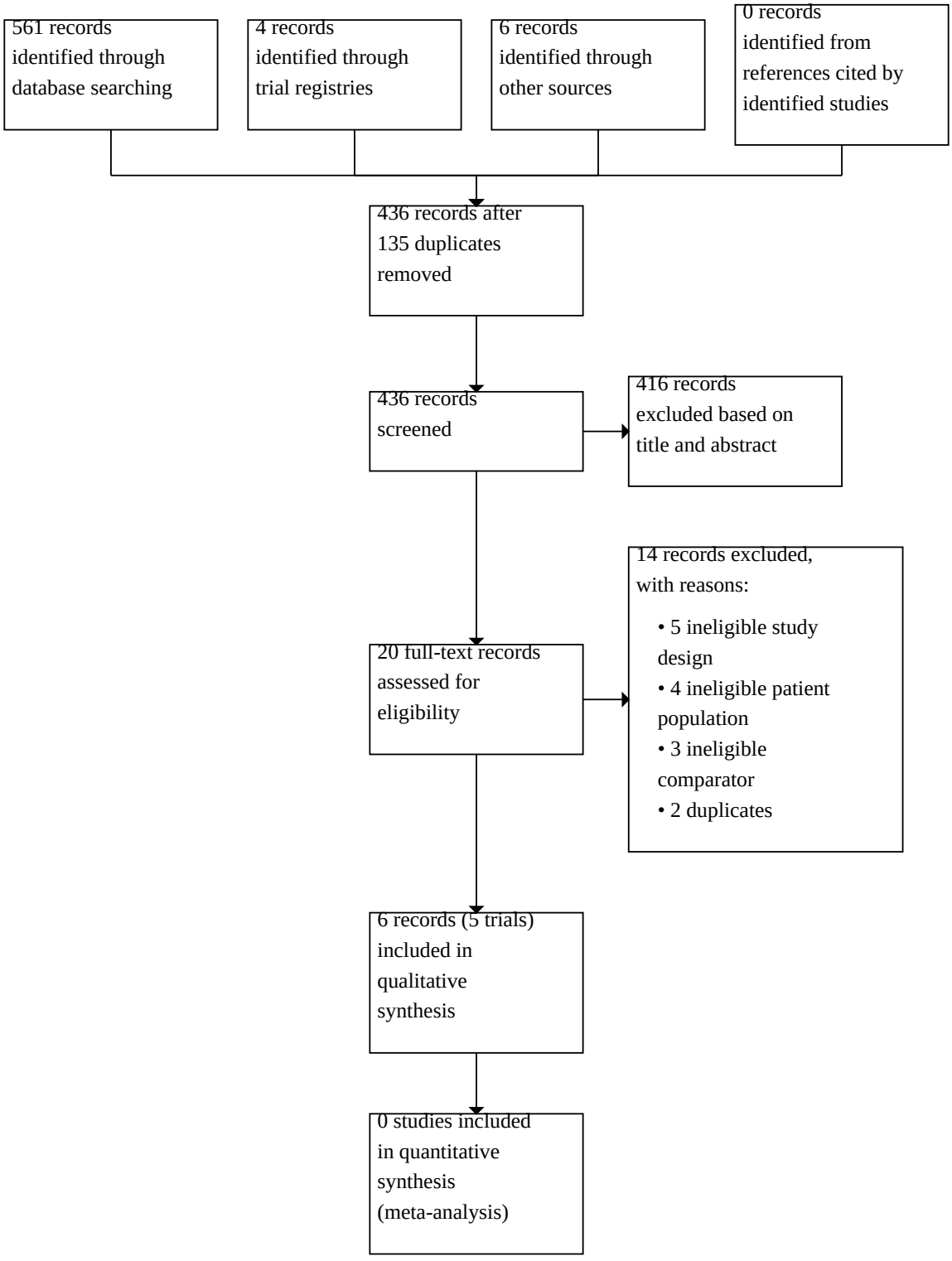
Data collection and analysis

We performed the review following Cochrane recommendations (Higgins 2021a). We used Covidence systematic review software for the analyses (Covidence). In case of disagreements between AMM and AC that could not be resolved by discussion, DT and NS served as arbitrators.

Selection of studies

Two review authors (AMM and AC) independently reviewed the titles and abstracts of trials identified by the searches and agreed on potential publications. We retrieved the full text of all apparently relevant trials. Two review authors (AMM and AC) independently assessed the full text of potential trials for inclusion in the review according to the prespecified criteria. We resolved differences in opinion by discussion. When we could not resolve the differences, we asked a third review author (NS) to provide an opinion. We kept a record of all included and excluded trials that were selected from the title review. We illustrated the trial selection process in a PRISMA flow diagram (Figure 1; Page 2021a; Page 2021b).

Figure 1. Study flow diagram (Page 2021a; Page 2021b). Date of search 17 February 2023.



We included reports of trials in languages other than English, providing we could obtain a reliable translation, following Cochrane recommendations (Higgins 2021a).

Data extraction and management

We designed a data collection form and piloted it on one of the identified potentially relevant trials. We then used the adapted form to record study characteristics from the trials potentially relevant for inclusion in terms of design, interventions, participants, and outcomes, as described in the Criteria for considering studies for this review section. Two review authors (AMM and AC) independently extracted the data. We resolved differences in extracted results by discussion, and when there was no agreement, a third review author (NS) provided an opinion.

Assessment of risk of bias in included studies

Two review authors (DT and AMM) were to independently assess the risk of bias in all five identified trials that would have fulfilled the inclusion criteria of our review if the review outcomes were reported. However, only one of the five trials reported an outcome of interest to our review, and hence, the two review authors assessed the risk of bias in that trial.

We resolved disagreements by consensus. We assessed risk of bias using the RoB 2 tool (Higgins 2021c; Sterne 2019), according to the domains defined in the MECIR protocol reporting standard 27 (Higgins 2021d) and methodological studies (Kjaergard 2001; Moher 2009; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008). We used the RoB 2 tool when assessing the effect of assignment to the intervention (Higgins 2021c; Sterne 2019).

We used the following five domains to assess bias in the individually randomised trials, including cross-over trials (Higgins 2021b; Higgins 2021c):

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of an outcome;
- bias in selection of the reported result.

For trials that allocated clusters of individuals, we would have included a sixth domain specific to the trial design to assess bias (i.e. bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation) (Eldridge 2021).

We assigned one of the three levels of judgement to an overall rating as follows (Naing 2020):

- low risk of bias: the trial was judged at low risk of bias for all domains for this result;
- some concerns: the trial was judged to raise some concerns in at least one domain for this result, but was not at high risk of bias for any of the remaining domains;
- high risk of bias: the trial was judged at high risk of bias in at least one domain for this result, or the study was judged to have some concerns for multiple domains in a way that substantially lowered confidence in the result.

The overall risk of bias judgement was the same as for individual domains, that is, low risk of bias, some concerns, or high risk of bias. Judging a result to be at a particular level of risk of bias for an individual domain implied that the result had an overall risk of bias at least this severe.

We used the RoB 2 Microsoft Word tool to store the data and to publish them in an online repository. The RoB 2 Microsoft Word tool allows inclusion of the rationale for each judgement for each signalling question for each study result (RoB 2 Tool; Sterne 2019).

We focused on results of the trials that contributed information that users of the review will find most useful. Therefore, we planned to present the following outcomes in the summary of findings table:

- all-cause mortality;
- proportion of participants with serious adverse events;
- health-related quality of life.

We did not modify the RoB 2 tool.

Measures of treatment effect

We intended to analyse dichotomous data using risk ratios, converting odds ratios to risk ratios using the standard formula (Higgins 2023), and to report risk ratios with 95% confidence intervals (CIs). We planned to analyse outcomes measured as continuous data, such as participant-reported data that used a 100-mm visual analogue scale (Walker 2020), using means and mean differences with their corresponding standard deviations and standard errors, and report these with 95% CIs. Where medians were stated, we intended to calculate median differences with 95% CIs using the Hodge-Lehmann estimator (Staffa 2020) and to consider baseline data and data from all available postintervention time points. However, the trials included no suitable data.

Unit of analysis issues

Each participant as randomised was the unit of analysis in each trial. We considered randomised clinical trials that had a parallel-group design, in which participants were intended to remain in the group to which they were initially assigned. We considered trials with two or multiple arms eligible.

For trials with a non-standard design or multiple intervention groups, we planned to consider, for each trial, whether the groups of individuals were randomised together to the same intervention (e.g. cluster-randomised trials (Higgins 2021b)) and to consider the impact on the analysis of these clustering, matching, or other non-standard design features of the included trials using MECIR Box 6.2.a and MECIR Box 6.2.b (Higgins 2021d). However, the trials included no such interventions.

We also considered whether individuals underwent more than one intervention (e.g. cross-over trials or simultaneous treatment on each individual), or whether there were multiple observations for the same outcome, and outcome data at the longest follow-up were collected (e.g. repeated measurements at different time points) (Higgins 2021b).

Dealing with missing data

We tried to find data on all participants who were randomised, so that we could undertake intention-to-treat analyses, which would include all participants, regardless of adherence or complete

follow-up. In cases where outcome data for excluded participants were not published, we intended to contact the authors of the trial and request their original data. We planned to gather information on non-completing participants, including the time and reason for dropping out, as described by the trial authors, and to record this on the data collection form. However, due to the time elapsed since publication of the one included trial that contributed data, this was not possible. Where possible, we planned to incorporate multiple imputations into the analysis (Jakobsen 2017). In addition, we planned to perform 'worst-best case scenario' and 'best-worst case scenario' analyses for participants lost to follow-up as sensitivity analyses (Deeks 2021). A best-worst case analysis is where it is assumed that none of the dropouts lost from the experimental arm, but all the dropouts lost from the control arm experienced the outcome. A worst-best case analysis is where it is assumed that all dropouts were lost from the experimental arm, but none from the control arm experienced the outcome. Both types of analysis are based on all randomised participants. However, the trials included no such data.

Assessment of heterogeneity

We planned to assess statistical heterogeneity, which is the presence and extent of between-study variation (Higgins 2021d; Box 10.10.a) using the Chi^2 test. Where the P value was less than 0.1, we intended to assume there was significant heterogeneity, and to quantify heterogeneity using the I^2 statistic (DerSimonian 1986; Higgins 2002). If intervention trials are combined, errors may arise during the assessment of heterogeneity due to differences in units of analysis (e.g. trials involving cluster randomisation may differ in between-study heterogeneity compared to trials in which individuals are randomised). Although this possibility is largely unexplored, the need to distinguish between the two types of randomised trials has been highlighted (Nyström 2002). To address this, we planned to use a fixed-effect analysis of comparisons within a trial and then a random-effects analysis between trials.

Methodological heterogeneity, due to differences in how the individual trials are implemented, and clinical heterogeneity, due to differences in participant and intervention characteristics, including quantity and type of fat modification, contribute to the presence and magnitude of statistical heterogeneity (Higgins 2003). We intended to investigate these types of heterogeneity using subgroup analysis to investigate the following.

- Trials with participants with acute compared to chronic gallstone disease.
- Trials with participants with high body mass index compared to normal or low body mass index.
- Trials with participants who were malnourished compared to those who were adequately nourished or overnourished.
- Trials with participants with diabetes compared to participants with normoglycaemia.
- Trials with participants with gallstones composed of cholesterol compared to participants with gallstones composed of pigment.
- Trials with different quantitative modifications of dietary fat (e.g. maximum planned reduction in grams of total dietary fat per day of 50% or less compared to maximum planned reduction greater than 50%).
- Trials with different qualitative modifications of dietary fat (e.g. reduction in dietary cholesterol compared to reduction in saturated fat intake).

Assessment of reporting biases

If at least 10 trials were found, we planned to assess publication bias in terms of treatment effect against trial size by developing a funnel plot using Review Manager (Review Manager 2020), and to stratify the funnel plots by risk of bias if we had at least 10 trials for each level of bias (Sterne 2019). However, we identified fewer than 10 trials.

Data synthesis

Meta-analysis

We intended to conduct meta-analyses if there were sufficient data from the included trials. If data from included trials precluded meta-analysis, we planned to calculate the effect estimate and measure precision from the available statistics if possible (Higgins 2023); or to calculate the effect estimate and measure of precision for the same effect measure from the available statistics (Higgins 2023); or to transform effect measures (e.g. convert standardised mean differences to odds ratios (Deeks 2021)). If the heterogeneity in the data, interventions, and outcomes made this impossible, we planned to tabulate and visually display the results (McKenzie 2021), following the Synthesis Without Meta-analysis (SWiM) guidelines for systematic reviews without meta-analysis where this was possible (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

Where there were sufficient trials, we planned to investigate clinical heterogeneity by inspection of the funnel plot(s) (Sterne 2001). We intended to use a formal statistical test to examine differences amongst subgroups (Borenstein 2013). This procedure tests for heterogeneity across subgroup results. If there were sufficient data, and irrespective of the presence of any heterogeneity, we proposed to perform subgroup analyses (see Assessment of heterogeneity).

Sensitivity analysis

We intended to perform sensitivity analyses to examine the impact of the following factors on effect size if we identified a sufficient number of randomised trials:

- trials at high risk of bias;
- trial funding;
- size of trials (e.g. large trials having at least 300 participants (Sawata 2011));
- trials identified using the following filters: diagnostic criteria; language of publication; source of funding (industry compared to other);
- the impact of participant loss to follow-up by conducting 'worst-best case scenario' and 'best-worst case scenario' analyses (see descriptions provided in Dealing with missing data).

Trial Sequential Analysis

We planned to use Trial Sequential Analysis (TSA) to control the risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2017; Wetterslev 2008; Wetterslev 2017). We wanted to compare our GRADE assessment of imprecision with the TSA assessment of imprecision. We planned to calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to control for random errors (Wetterslev 2008; Wetterslev 2009). For

each TSA performed, we intended to calculate a diversity-adjusted required information size (DARIS), based on the intervention effect suggested by trials at a low risk of bias and an intervention effect of 20% risk reduction, a type I error risk of 2.0% (the conventional value of 5.0% divided by 3, rounded, because of our three primary outcomes), and a type II error risk of 10% (Wetterslev 2009). We planned to undertake DARIS using the observed diversity adjustment factor $1/(1 - D^2)$, the heterogeneity estimated by D^2 amongst all trials, and with an assumed final diversity of 50% (Wetterslev 2009). For continuous outcomes, we planned to use a minimal relevant difference equal to SD/2, where SD is the standard deviation of the control group; a type I error risk of 2.0%; and a type II error risk of 10%.

Summary of findings and assessment of the certainty of the evidence

We intended to use the GRADE approach to present data in a summary of findings tables as follows (GRADEpro GDT). We planned to present comparisons between the experimental interventions and the control interventions for each primary outcome, at the longest follow-up, presenting the range and mean or median, in a separate summary of findings table.

- All-cause mortality.
- Proportion of participants with serious adverse events at longest follow-up.
- Health-related quality of life, assessed using validated tests.

For each outcome, we intended to include the following information in each summary of findings table.

- The assumed risk; a measure of the typical burden of the outcomes (i.e. the illustrative risk, also called the baseline risk, baseline score, or control group risk).
- The corresponding risk; a measure of the burden of the outcomes after the intervention is applied (i.e. the risk of an outcome in treated/exposed people based on the relative magnitude of an effect and assumed (baseline) risk).
- The relative effect; for dichotomous outcomes, the table will provide the risk ratio, odds ratio, or hazard ratio.
- The number of participants, and the number of trials and their designs.
- Rating of the overall certainty of evidence for each outcome (which may vary by outcome).
- Footnotes or explanations, if needed, to provide explanations about information in the table.
- Comments.

We also planned to present the overall certainty of the evidence for the 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 the effect estimate (wide CIs (Jakobsen 2014) and risk of publication bias (GRADEpro GDT; Meader 2014)). Regarding risk of bias, we proposed to determine an overall judgement for each outcome taking into account the contribution of each study (e.g. larger trials with many events contributing more to the overall risk of bias than smaller trials). 'Low risk of bias' indicates 'no limitation (the certainty is not downgraded)'; 'some concerns' indicates either 'no limitation' or 'serious limitation (the certainty is downgraded one level)'; and 'high risk of bias' indicates either 'serious limitation' or 'very serious limitation (the certainty is downgraded two levels)'.

Two review authors (DT and AMM) planned to independently define the evidence as 'high', 'moderate', 'low', or 'very low' certainty. These levels are defined as follows (Schünemann 2013).

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

We resolved disagreements first by discussion, and if required, by consultation with a third review author (NS or AC).

RESULTS

Description of studies

Results of the search

We identified a total of 571 references by searching the databases and other resources as described in Electronic searches (17 February 2023) and Searching other resources (March 2023). We identified 561 references through electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (12 records), CENTRAL (75 records), MEDLINE ALL (80 records), Embase (348 records), LILACS (10 records), and Science Citation Index Expanded and Conference Proceedings Citation Index – Science (36 records). We identified four records by searching trial registries which comprised ClinicalTrials.gov (four records), WHO ICTRP (zero records), and European Medicines Agency (zero records). We found no records from searching pharmaceutical company sources. We identified six records from other sources. These included three records identified by searching System for Information on Grey Literature in Europe OpenGrey (zero records) and Data Archiving and Networking Services (as an archive from OpenGrey) (three records) and three records from citations of our original protocol (Madden 2017). No further records were identified from references cited by identified studies. After removing 135 duplicate records, we screened 436 references. We excluded 416 clearly irrelevant references based on the titles and abstracts. We retrieved 20 full-text records for further assessment. We excluded 14 records for the reasons stated in the Characteristics of excluded studies table. Therefore, we included five trials described in six records (see Characteristics of included studies table).

The reference flow is shown in the PRISMA flow diagram (Figure 1; Page 2021a; Page 2021b).

Included studies

We included five trials (Burnand 2016; Lee 1985; Lefkof 1986; Maudgal 1978; Maudgal 1982). One trial was reported in two references which described the same participants and intervention but different outcomes and analyses were reported (Frenkiel

1986, see Lefkof 1986; Lefkof 1986). The five trials randomised 132 participants to different interventions. These include 69 participants who took part in two studies (Frenkiel 1986, see Lefkof 1986; Lefkof 1986) and a subgroup of 12 of the 69 who also took part in Lee 1985. The number of participants in the trials ranged from seven to 69. Only one trial with 69 participants reported one of the systematic review outcomes (Lefkof 1986).

We had planned to include cross-over trials but to use only data from the first trial period to avoid residual effects from the intervention (Higgins 2021a; Higgins 2021b). Three were cross-over trials and none reported the results from the first trial period separately (Lee 1985; Maudgal 1978; Maudgal 1982). The findings from these trials were included because the length of each arm of the dietary intervention was at least three weeks (three weeks, Lee 1985; one month, Maudgal 1978; three months, Maudgal 1982), which was probably long enough for carryover effects to disappear. This was recorded during the assessment of risk of bias, resulting in this domain being considered of some concern for bias for all three trials and this was also noted in the Differences between protocol and review section. The search identified no cluster-randomised trials. Further summary details of the included trials are available in Table 1.

Four trials were published between 1978 and 1986 and the most recent trial was published in 2016. The trials were undertaken in the UK (Maudgal 1978; Maudgal 1982; Burnand 2016) or USA (Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986). One trial had a protocol that was published as supplementary data with the findings (Burnand 2016).

We contacted one corresponding author who responded with additional information including the study protocol, but it did not have data on the outcomes we required (Burnand 2016). We searched for current contact details for the corresponding authors of three other reports that were published between 1978 and 1986 but were unable to correspond with them (Lee 1985; Maudgal 1978; Maudgal 1982).

Only one of the five included trials reported on one outcome of this systematic review, which is described in more detail below (Lefkof 1986).

Participants

The mean age of participants was 53.7 (SD 10.9) years. Male and female adults were included, and the proportion of females was 54%. The mean percentage ideal bodyweight was 109.4% (SD 17.9%). The diagnosis of gallstones was made using radiolucent methods, but the exact method used to identify gallstones was not described.

Experimental interventions

The experimental dietary interventions in the included trial were a low-cholesterol diet (250 mg/day) (19 participants) and medium-chain triglyceride substitution (20% of dietary fat) diet (16 participants).

The 17 remaining participants were randomised to an experimental diet using bran, which was outside the inclusion criteria for this systematic review.

Control intervention

The control intervention was a control diet comprising a standard intake providing 500 mg/day to 600 mg/day of cholesterol (17 participants).

Co-interventions

All participants received ursodeoxycholic acid during the trial and the dose and timing of its administration were identical in the experimental dietary intervention groups and the control group.

Follow-up

The intervention lasted for 21 months with a follow-up assessment of gallstone dissolution made after "nine months or 21 months" (the exact time of the follow-up assessment was unclear and not identified by the authors). The number of participants assessed at 21 months was not reported. The follow-up results for dissolution of gallstones for both time periods were presented together.

Withdrawals

Four participants (21.1%) from the low-cholesterol group, three (18.8%) from the medium-chain triglyceride substitution group, and three (17.6%) from the control group dropped out of the trial.

Funding

The included trial was funded by a governmental grant (NIH Grant AM 15631) and the authors reported that they received no funding that could have biased the trial results through conflicts of interest.

The trial was published in 1986 and was undertaken in the USA. There was no study protocol available.

Excluded studies

Five studies were not randomised clinical trials or did not include sufficient information to confirm their study design even after contacting the authors (Grundy 1987; Kern 1994; Rumessen 2005; Stokes 2014b; Yago 2005).

Four studies were excluded because the study population did not include participants with gallstones, data from participants with gallstones could not be analysed separately from those without gallstones, or gallstones were not diagnosed radiologically (de Menezes 2013; Gebhard 1996; Lean 2018; Mogadam 1984).

Three studies investigated a comparator that was not relevant to this systematic review (ChiCTR1900021184; Kupfer 1982; Kurbanov 2003).

Two reports were duplicates (Burr 2014; Stokes 2014a).

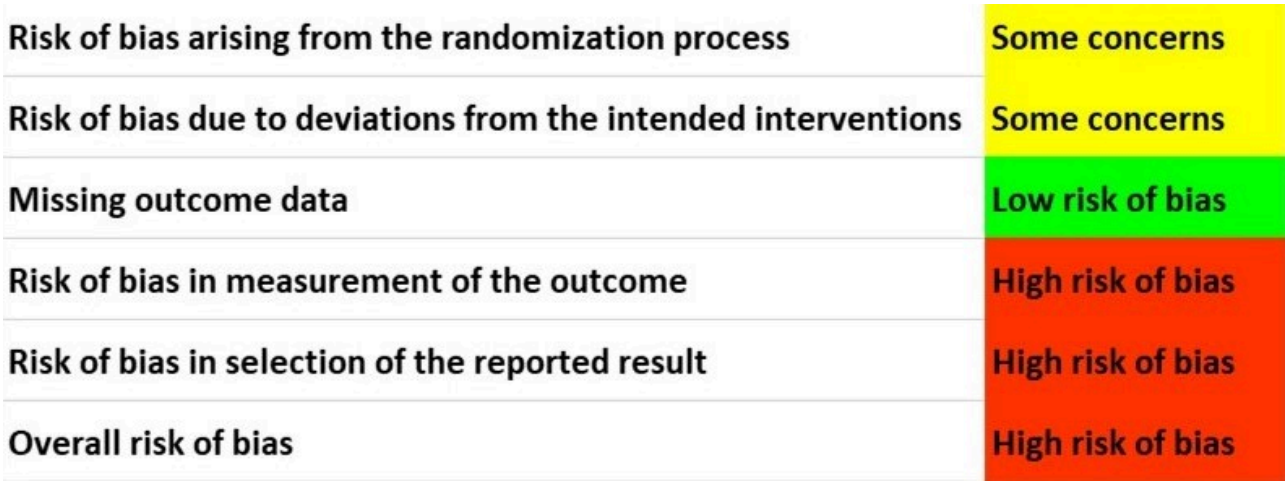
Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

We assessed the included trial that provided data for the review at an overall high risk of bias (Lefkof 1986). The risk of bias is summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for the included study that reported a secondary outcome of the systematic review (Lefkof 1986).



Domain 1: risk of bias arising from the randomisation process: the included trial that provided data for the review was described as randomised, but the methods used for sequence generation and concealing the allocation sequence were not described, and as a result, it was considered to have some concern about the risk of bias (Lefkof 1986).

Domain 2: risk of bias due to deviations from the intended interventions (effect of assignment to intervention): the included trial that provided data for the review did not describe the intended intervention sufficiently, with no information provided about who delivered the dietary intervention, and as a result, it was considered to have some concern about the risk of bias (Lefkof 1986).

Domain 3: missing outcome data: the included trial that provided data for the review described outcome data for all participants and no participants were unaccounted for, and as a result, it was considered at low risk of bias (Lefkof 1986).

Domain 4: risk of bias in the measurement of the outcome: the included trial that provided data for the review did not describe adequately the assessment of gallstone dissolution, which was based on the number of participants categorised with complete, partial, or non-dissolution of gallstones. The definitions for dissolution categories were based on the percentage reduction in gallstone volume, but the variation in volume between participants was substantial (mean volume pre-intervention for all participants 17.0 (SD 34.9) cm^3), and as a result, it was considered at high risk of bias (Lefkof 1986).

Domain 5: risk of bias in selection of the reported result: the included trial that provided data for the review did not describe a prespecified analysis plan and there was no trial protocol. The trial did not adequately describe the time points for the data presented on the dissolution of gallstones, and as a result, it was considered at high risk of bias (Lefkof 1986).

Effects of interventions

See: **Summary of findings 1** Modified dietary fat intake for treatment of gallstone disease in people of any age

Primary outcomes

All-cause mortality

The trials did not report data on all-cause mortality.

Proportions of participants with serious adverse events

One trial described surgical interventions in participants with eight participants withdrawing from the trial because they underwent cholecystectomy, but the trial authors did not report whether these were participants in the control or intervention groups (Lefkof 1986). The other four trials did not report data on any other serious adverse events associated with the intervention.

Health-related quality of life assessed using validated test

The trials did not report data on health-related quality of life.

Secondary outcomes

Proportion of participants without dissolution or reduction in size of gallstones

One trial reported the reduction in the size of gallstones as the number of participants with complete, partial, or non-dissolution of gallstones and found no differences between participants taking a standard diet, a low-cholesterol diet (250 mg or less), or a diet containing 20% of energy as medium-chain triglyceride, assessed using oral cholecystography after nine or 21 months of intervention (Lefkof 1986). The other four trials did not report data on dissolution or reduction in size of gallstones.

Proportion of participants with non-serious adverse events

We found no data on the proportion of participants with non-serious adverse events in the included trials.

We found no harm due to the experimental interventions reported in any of the excluded studies identified with the searches for randomised clinical trials, including the randomised trials not reporting any outcomes for this systematic review.

We were unable to apply the SWiM reporting approach (Campbell 2020) for narrative reporting of the outcome described in Lefkof 1986 because no other trials were included.

We were unable to apply the GRADE approach to determine certainty of evidence because the included trial that reported data on one of the review outcomes did not provide data that could be used to generate an estimate of the effect on the outcomes predefined in the systematic review (Schünemann 2013). Therefore, we were unable to complete the summary of findings table.

DISCUSSION

Summary of main results

We performed a systematic review of modified dietary fat interventions for gallstone disease. We included five trials, but only one trial (69 participants) reported a secondary outcome of the systematic review and, therefore, it was not possible to perform a meta-analysis. This trial reported that eight participants withdrew due to surgery (considered a serious adverse event and therefore a primary outcome), but did not state if these were in the intervention or control group. No other trials included data relating to the primary outcomes of this review. One trial investigated a secondary outcome, dissolution or reduction in size of gallstones, which reported no differences between groups taking a standard diet, a low-cholesterol diet, or a diet supplemented with medium-chain triglycerides. No other trials included data relating to the two secondary outcomes of this review.

The objective of this systematic review was to evaluate the benefits and harms of modified dietary fat intake in the treatment of gallstone disease, but we could not address this from the evidence identified and, therefore, there is considerable uncertainty about this treatment.

Overall completeness and applicability of evidence

We included all eligible randomised clinical trials up to 17 February 2023. This enabled us to consider early papers. This led to the inclusion of five trials that were published between seven and 45 years ago and the implications of this are discussed in the Quality of the evidence section. We intended to include participants with gallstone diagnosis confirmed by ultrasound. However, four included trials were published before ultrasound became widely available (Lee 1985; Lefkof 1986; Maudgal 1978; Maudgal 1982), so we included participants whose gallstones were conclusively diagnosed using imaging methods (see Differences between protocol and review). We planned to evaluate outcomes at the longest period of follow-up to enable us to consider the long-term dietary effects, but the time point for assessing dissolution of gallstone in the one trial that reported this outcome was unclear.

We reviewed the observational studies identified by the searches for harms and did not identify any that described harms relating to the modification of dietary fat intake. Most observational studies described case-control comparisons of people with gallstones and controls who did not and these studies identified characteristics that differed between the groups including dietary intake, physical activity, body mass index, and meal frequency (e.g. Gonzalez-Hita 2014; Kiani 2020; Misciagna 1999). While these provide insight into risk factors for developing gallstones and the potential to develop prevention strategies, they do not address the issue of dietary management for those who have gallstones. It is worth noting one study by Festi and colleagues, which investigated the effect of weight-reducing diets providing different amounts of dietary fat (3.0 g of fat per day versus 12.2 g of fat per day) on gallbladder motility in people with obesity but without gallstones (Festi 1998). They reported that significantly more gallstones developed in people on the 3.0 g fat regimen than on the regimen containing more fat (6/11 with 3.0 g/day of fat versus 0/11 with 12.2 g/day of fat; $P < 0.01$). They concluded that this was probably due to the 12.2 g/day fat diet helping to maintain adequate gallbladder motility. This should be contextualised in that 12.2 g/day fat is considered a very low-fat intake for an adult with most consuming diets providing greater than 30 g/day and many consuming considerably more than this.

The findings of this review, which are limited by lack of evidence, are applicable to modification of dietary fat intake in confirmed gallstone disease, and we have found no evidence to support or refute any effects.

Quality of the evidence

This review followed the overall plan of our published peer-reviewed Cochrane protocol (Madden 2021). Some parts of the protocol were modified in response to the changes to clinical trial registries and to allow the findings from early trials to be considered (see Differences between protocol and review). We conducted a thorough review in accordance with Cochrane methodology (Higgins 2021a), and we implemented the findings of methodological studies (Kjaergard 2001; Moher 2009; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008).

Four trials included in this systematic review were published more than 36 years ago (Lee 1985; Lefkof 1986; Maudgal 1978; Maudgal 1982). Although the papers reporting these trials met the inclusion criteria of the review, their description of the research was incomplete compared to the CONSORT statement (Schulz 2010), and were of some concern or high risk of bias. In addition, there were discrepancies between and within the report of the included trial (Lefkof 1986), and another paper, describing the same intervention but reporting different outcomes (Frenkiel 1986, see Lefkof 1986). These discrepancies included differences in the numbers reported in each participant group and reported in tables.

In addition, four trials modified dietary fat intake by reducing dietary cholesterol. At the time of their publication, low-cholesterol diets were frequently used in clinical practice to treat high blood cholesterol concentrations (AHA Nutrition Committee 2006), but this is no longer considered to be the optimum dietary treatment (Berger 2015). A current understanding of lipid metabolism is that components of blood cholesterol concentrations are influenced by other dietary factors, including total and saturated fat and refined carbohydrate (Pearson 2021), and also reflect endogenous cholesterol synthesis rather than being dependent solely on dietary cholesterol. It is also understood that the relationship between blood and biliary cholesterol concentrations is not linear with values being influenced by both dietary intake (Di Ciaula 2013) and diurnal variation in cholesterol and bile acid synthesis (Schroor 2019). As a result, the interventions used in the included trials (i.e. reducing dietary cholesterol in the absence of controlling for other components of dietary fat) are no longer considered valid (EASL 2016). It is important to note that the trials, which were undertaken over months and involved invasive methods to obtain biliary samples for laboratory analysis, did not evaluate participants' symptoms, clinical well-being, or quality of life. In

addition, the ethnicity, socioeconomic status, and metabolic status of participants were not reported.

Potential biases in the review process

The strengths of the systematic review process include the range of databases covered and the inclusion of trials irrespective of language of publication or participant age.

We excluded studies where participants with gallstones were also diagnosed with another condition that might compromise dietary fat tolerance (e.g. cholestatic liver disease, short bowel, intestinal failure, or pancreatic insufficiency), unless data from participants without these conditions could be analysed separately. As a result, the findings from this review are not applicable to people with gallstones who have any of these conditions. We included only randomised clinical trials due to their value in identifying benefits from intervention, and we did not conduct separate searches for observational studies on harms. Randomised clinical trials may not collect or report harms in a detailed manner and as a result, our findings may be biased toward the benefits of modifying dietary fat intake with less focus on harms (Bjelakovic 2021; Buzzetti 2021).

We intended to include trials with no restriction on the age of participants. The included trials evaluated only adults. We identified no trials with children. Although gallstone disease has been considered to be a condition mainly affecting adults, there is an increasing incidence of gallstones in children reported (Goldman 2020). The findings of this review are not applicable to children.

Agreements and disagreements with other studies or reviews

One systematic review examined the effects of higher dietary fat intake and ursodeoxycholic acid in the prevention of gallstones in adults who were losing weight (Stokes 2014). They concluded that this intervention appears to prevent the formation of gallstones. By contrast, our systematic review examined the effects of dietary fat modification in people with existing gallstones. Therefore, ours is the first systematic review on the impact of dietary intervention on clinical outcomes with gallstone disease, and we are unable to compare our conclusions with those of other reviews.

AUTHORS' CONCLUSIONS

Implications for practice

While there are general health benefits associated with avoiding excessive dietary fat (i.e. reduced risk of obesity and cardiovascular disease), the evidence in this review indicates uncertainty about the effects of the modification of dietary fat intake in people with gallstone disease. We do not know if modifying dietary fat, compared with no dietary intervention, may increase or reduce all-cause mortality, serious adverse events, health-related quality of life, dissolution or reduction in size of gallstones, and non-serious adverse events in people with gallstones.

Implications for research

Much more evidence is needed in order to establish the beneficial and harmful effects of modifying dietary fat on gallstone disease.

There is a need for high-quality randomised clinical trials evaluating the health effects of low-fat diets and diets with levels of total fat intake that are comparable with current guidelines for a healthy intake (i.e. approximately 30% to 35% total energy intake) in people with gallstones. Intakes of refined carbohydrates and dietary fibre, as well as the consumption of breakfast and the frequency of food consumption, should be controlled for or co-investigated because of the potential impact on stone formation or gallbladder emptying.

Characteristics that are risk factors for gallstones, including age, sex, ethnicity, socioeconomic status, and the presence of comorbidities such as intestinal or liver disease and metabolic disorders, should be reported and, where possible, controlled for and subgroup analyses undertaken. This is to ensure that findings are equitable to all (e.g. women who are at higher risk of gallstones and are more likely to take responsibility for food-related activities and so may be impacted by dietary modification).

Outcomes measured should include objective symptomatic response to food intake, health-related quality of life, episodes of cholecystectomy, progression to cholecystectomy, and other outcomes that are of concern to people with gallstones.

Comprehensive measurement and reporting of harms should be undertaken to enable a holistic view of the effects of the intervention.

Future trials should be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) statement (www.spirit-statement.org), and reported according to the CONSORT statement (www.consort-statement.org,) including methodological reporting according to STROBE-nut, items 5 to 17 (STrengthening the Reporting of OBservational studies in Epidemiology – nutritional epidemiology extension; Hörnell 2017; Lechat 2016).

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- Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor CHBG, Denmark

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Associate Editor (protocol screening): Leslie Choi, Evidence Production and Methods Department, Cochrane, UK

Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Burnand 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	46 adults (42 female; 4 male) with gallstones
Interventions	Low-calorie diet with reduced fat intake: 800 kcal/day including median 16 (range 10–35) g fat
Outcomes	Primary outcome: operative time measured from first incision to end of skin closure
Notes	No data on any of the systematic review primary or secondary outcomes.

Lee 1985

Study characteristics	
Methods	Crossover randomised clinical trial
Participants	12 adults (6 female; 6 male) with gallstones
Interventions	3 dietary interventions • Cholesterol intake: 500 mg/day • Cholesterol intake: 750 mg/day • Cholesterol intake: 1000 mg/day
Outcomes	Primary outcome not stated
Notes	No data on any of the systematic review primary or secondary outcomes.

Lefkof 1986

Study characteristics	
Methods	Randomised clinical trial
Participants	69 adults (37 female; 32 male) with gallstones; same participants as in paper by Frenkiel 1986
Interventions	4 dietary interventions • Standard cholesterol 500 mg/day • Low cholesterol 250 mg/day • Bran-supplementation (30 g/day) *excluded from the review* • Medium-chain triglyceride oil substitution (20% of fat energy) All participants also received ursodeoxycholic acid 750 mg
Outcomes	Primary outcome not stated

Lefkof 1986 *(Continued)*

Notes	Lefkof 1986 had 2 publications: Frenkiel 1986 and Lefkof 1986. **Frenkiel 1986** No data on any of the systematic review primary or secondary outcomes Participants in Frenkiel 1986 were the same participants and received the same interventions as in Lefkof 1986 **Lefkof 1986** 69 adults (37 female; 32 male) with gallstones; same participants as in paper by Frenkiel 1986 *Interventions* 4 dietary interventions • Standard cholesterol 500 mg/day • Low cholesterol 250 mg/day • Bran-supplementation (30 g/day) *excluded from the review* • Medium-chain triglyceride oil substitution (20% of fat energy) All participants in all groups also received UDCA 750 mg/day. *Outcomes* Primary outcome not stated *Notes* No data on any of the systematic review primary outcomes Only 1 review secondary outcome reported (i.e. numbers of participants in 4 categories of dissolution of gallstones) (below gives the details for the 3 interventions of interest to the review): • Standard diet (17 participants): 4 = complete dissolution; 3 = partial dissolution; 7 = non-dissolution; 3 = withdrawn. • Low-cholesterol diet (19 participants): 4 = complete dissolution; 2 = partial dissolution; 9 = non-dissolution; 4 = withdrawn. • Medium-chain triglyceride supplemented diet (16 participants): 4 = complete dissolution; 5 = partial dissolution; 4 = non-dissolution; 3 = withdrawn. Overall comparison between the groups using Fisher's exact test, P = 0.793. The trial was funded by a governmental grant (NIH Grant AM 15631) and the authors reported that they received no funding that could have biased the trial results through conflicts of interest. The trial was published in 1986 and was undertaken in the USA. There was no study protocol available.

Maudgal 1978

Study characteristics	
Methods	Crossover randomised clinical trial
Participants	7 adults (6 female; 1 male) with gallstones
Interventions	Cholesterol intake: 100 mg/day

Maudgal 1978 *(Continued)*

Outcomes	Primary outcome not stated
Notes	No data on any of the systematic review primary or secondary outcomes.

Maudgal 1982

Study characteristics	
Methods	Crossover randomised clinical trial
Participants	10 adults (6 female; 4 male) with gallstones
Interventions	Cholesterol intake: 100 mg/day
Outcomes	Primary outcome not stated
Notes	No data on any of the systematic review primary or secondary outcomes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Burr 2014	Abstract. Duplicate publication of the randomised clinical trial by Burnand 2016 (included study) confirmed by corresponding author (3 September 2021).
ChiCTR1900021184	Ineligible comparator: entry on trial registry reports that both groups would receive low-fat diets
de Menezes 2013	Ineligible patient population: postcholecystectomy and no biliary gallstones
Gebhard 1996	Ineligible patient population: healthy participants with normal gallbladders
Grundy 1987	Ineligible study design: report of meeting; not a randomised clinical trial
Kern 1994	Ineligible study design: participants with gallstones were not randomised to dietary intervention
Kupfer 1982	Randomised clinical trial, but ineligible comparator: participants with gallstones were randomised to drug and dietary intervention and not possible to extract data on only dietary intervention
Kurbanov 2003	Ineligible comparator: both groups received 65 g of fat
Lean 2018	Ineligible patient population: participants did not have gallstones
Mogadam 1984	Ineligible patient population: only 1 participant had gallstones
Rumessen 2005	Ineligible study design: discussion about postcholecystectomy treatment. Not a randomised clinical trial
Stokes 2014a	Abstract duplicate of Stokes 2014b (excluded study)
Stokes 2014b	Ineligible study design: systematic review and meta-analysis

Study	Reason for exclusion
Yago 2005	Ineligible study design: participants were not randomised but allocated to intervention on the basis of their dietary habits

ADDITIONAL TABLES

Table 1. Summary of characteristics of five included trials[a]

Variable	Summary
Study design	2 trials were single-centre, randomised clinical trials with 2 arms (Burnand 2016) or 3 arms (Frenkiel 1986, see Lefkof 1986; Lefkof 1986). 3 trials were single-centre crossover trials where participants were randomised to either 3 (Maudgal 1982, Lee 1985) or 4 diets (Maudgal 1978).
Participant characteristics	The mean or median age of participants in the trials ranged from 43.5 to 56.3 years in the trials that reported this information (Maudgal 1982; Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986; Burnand 2016). All 5 trials included male and female participants and the proportion of female participants ranged from 50% to 91%. Only 1 trial reported participants' initial mean body mass index and this was 33.8 kg/m^2 (Burnand 2016). 3 trials reported participants' percent ideal bodyweight and this ranged from 106% to 109% (Maudgal 1982; Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986). 1 trial did not report body mass index, percent ideal bodyweight, or actual bodyweight (Maudgal 1978). All 5 trials diagnosed gallstones using radiolucent methods (Maudgal 1978; Maudgal 1982; Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986; Burnand 2016). Two trials specified diagnosis was made using oral cholecystography (Maudgal 1978; Maudgal 1982), and in one trial, the author confirmed diagnosis was made using ultrasound (Burnand 2016). Two trials did not describe the method used to identify radiolucent gallstones (Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986).
Interventions compared	The dietary interventions in these 5 trials investigated the effects of: • very low calorie diet with reduced fat intake (Burnand 2016) • low cholesterol with CDCA (Maudgal 1978; Maudgal 1982) • low cholesterol with UCDA (Frenkiel 1986, see Lefkof 1986; Lefkof 1986) • low cholesterol with CDCA with plant sterols (Maudgal 1978) • modified cholesterol (Lee 1985) • medium-chain triglyceride substitution with UDCA (Frenkiel 1986, see Lefkof 1986; Lefkof 1986) • plant sterol supplementation with CDCA (Maudgal 1978) The intervention diets were compared with a "normal diet" which was either the participants' habitual, unmodified diet (Burnand 2016), or a standard diet providing cholesterol 500–600 mg (Maudgal 1978; Maudgal 1982; Lee 1985; Lefkof 1986). In trials that included CDCA or UDCA as co-interventions, the dose and timing of the medication was identical in the normal diet and dietary intervention.
Intervention duration and follow-up	Interventions lasted for 2 weeks (Burnand 2016), 9 weeks (i.e. 3 diets for 3 weeks each) (Lee 1985), 4 months (i.e. 4 diets for 1 month each) (Maudgal 1978), 6 months (i.e. 2 diets for 3 months each) (Maudgal 1982), and 21 months (Frenkiel 1986, see Lefkof 1986; Lefkof 1986).

Table 1. Summary of characteristics of five included trials[a] *(Continued)*

Trials reporting outcomes	1 trial reported the dissolution of gallstones which was a secondary outcome for this review (Lefkof 1986). 4 trials reported the cholesterol saturation of bile (saturation index) (Maudgal 1978; Maudgal 1982; Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986). 1 trial reported the kinetics of bile acid (total bile acid pool) and secretion of biliary lipids (cholesterol) (Frenkiel 1986, see Lefkof 1986). 1 trial reported the operative time at cholecystectomy, weight change, complications after cholecystectomy, length of stay after cholecystectomy, day case rate at cholecystectomy, perceived difficulty of cholecystectomy procedure (Burnand 2016).
Funding	2 trials were supported by NIH Grant AM 15631 (Lee 1985; Frenkiel 1986, see Lefkof 1986; Lefkof 1986). 2 trials were supported by finance from Weddel Pharmaceuticals (Maudgal 1978; Maudgal 1982), and 1 of them was also supported by finance received from St George's Hospital medical research committee and with plant sterols received from Eli Lilly Company Ltd (Maudgal 1978). 1 trial received no funding (Burnand 2016).
Overall risk of bias	1 trial was at low overall risk of bias (Burnand 2016). 1 trial was judged to be of some concerns (Lee 1985). 3 trials were at high overall risk of bias (Frenkiel 1986, see Lefkof 1986; Lefkof 1986; Maudgal 1978; Maudgal 1982).

[a]Five trials were reported in six references. Frenkiel 1986 (see Lefkof 1986) and Lefkof 1986 report one trial with the same participants and intervention but different outcomes and analysis.
CDCA: choledeoxycholic acid; UDCA: ursodeoxycholic acid.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register (searched via the Cochrane Register of Studies Web)	17 February 2023	(diet* AND fat* AND (restrict* OR modif* or reduc* or low* or high*)) AND (cholelithiasis or gallstone* or gall-stone* or ((gall or gall bladder or gallbladder) and stone*))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2023, Issue 2	#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 MeSH descriptor: [Diet, High-Fat] explode all trees #5 diet* and fat* and (restrict* OR modif* or reduc* or low* or high*) #6 #1 or #2 or #3 or #4 or #5

(Continued)

		#7 MeSH descriptor: [Cholelithiasis] explode all trees #8 cholelithiasis or gallstone* or gall-stone* or ((gall* or gall bladder or gall-bladder) and stone*) #9 #7 or #8 #10 #6 and #9
MEDLINE ALL Ovid	1946 to 17 February 2023	1. exp Nutrition Therapy/ 2. exp Dietary Fats/ 3. exp Diet, Fat-Restricted/ 4. exp Diet, High-Fat/ 5. (diet* and fat* and (restrict* or modif* or reduc* or low* or high*)).mp. 6. 1 or 2 or 3 or 4 or 5 7. exp Cholelithiasis/ 8. (cholelithiasis or gallstone* or gall-stone* or ((gall or gall bladder or gall-bladder) and stone*)).mp. 9. 7 or 8 10. 6 and 9 11. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. 12. clinical trials as topic.sh. 13. (random* or placebo*).ab. or trial.ti. 14. 11 or 12 or 13 15. exp animals/ not humans.sh. 16. 14 not 15 17. 10 and 16
Embase Ovid	1974 to 17 February 2023	1. exp diet therapy/ 2. exp fat intake/ 3. exp lipid diet/ 4. (diet* and fat* and (restrict* or modif* or reduc* or low* or high*)).mp. 5. 1 or 2 or 3 or 4 6. exp cholelithiasis/ 7. (cholelithiasis or gallstone* or gall-stone* or ((gall or gall bladder or gall-bladder) and stone*)).mp. 8. 6 or 7 9. 5 and 8

(Continued)

Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or retracted article/

11. (random$ or placebo or parallel group$1 or crossover or cross over or assigned or allocated or volunteer or volunteers).ti,ab.

12. (compare or compared or comparison or trial).ti.

13. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

14. (open adj label).ti,ab.

15. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

16. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

17. (controlled adj7 (study or design or trial)).ti,ab.

18. (erratum or tombstone).pt. or yes.ne.

19. or/10-18

20. (random$ adj sampl$ adj7 ('cross section$' or questionnaire$ or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

21. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

22. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

23. (Systematic review not (trial or study)).ti.

24. (nonrandom$ not random$).ti,ab.

25. 'Random field$'.ti,ab.

26. (random cluster adj3 sampl$).ti,ab.

27. (review.ab. and review.pt.) not trial.ti.

28. 'we searched'.ab. and (review.ti. or review.pt.)

29. 'update review'.ab.

30. (databases adj4 searched).ab.

31. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

32. Animal experiment/ not (human experiment/ or human/)

33. or/20-32

34. 19 not 33

35. 9 and 34

(Continued)

LILACS (Virtual Health Library Regional Portal)	1982 to 17 February 2023	((diet* AND fat* AND (restrict* OR modif* OR reduc* OR low* OR high*))) AND ((cholelithiasis OR gallstone* OR gall-stone* OR ((gall* OR gall bladder OR gallbladder) AND stone*))) AND (db:("LILACS"))
Science Citation Index Expanded (Web of Science)	1900 to 17 February 2023	# 5 #4 AND #3 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) # 3 #2 AND #1 # 2 TS=(cholelithiasis or gallstone* or gall-stone* or ((gall* or gall bladder or gallbladder) and stone*)) # 1 TS=(diet* and fat* and (restrict* OR modif* or reduc* or low* or high*))
Conference Proceedings Citation Index – Science (Web of Science)	1990 to 17 February 2023	# 5 #4 AND #3 # 4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) # 3 #2 AND #1 # 2 TS=(cholelithiasis or gallstone* or gall-stone* or ((gall* or gall bladder or gallbladder) and stone*)) # 1 TS=(diet* and fat* and (restrict* OR modif* or reduc* or low* or high*))
ClinicalTrials.gov (clinicaltrials.gov/)	March 2023	Cholelithiases, gall stone, gallstone
European Union Clinical Trials Registry (EU CTR www.clinicaltrialsregister.eu/ctr-search/search)	March 2023	Cholelithiasis OR gallstone OR gallstones OR gall
World Health Organization International Clinical Trial Registry Platform (WHO ICTRP trialsearch.who.int/)	March 2023	Cholelithiasis OR gallstone OR gallstones OR gall
Pharmaceutical company sources, for ongoing or unpublished trials	March 2023	10 pharmaceutical companies were identified on the basis of their high market value (www.pharmaceutical-technology.com/comment/top-20-biopharmaceutical-companies/) and each company's website searched for trials using terms cholelithiasis, gallstone, gallstones and gall
System for Information on Grey Literature in Europe OpenGrey (www.opengrey.eu and its archive easy.dans.knaw.nl/ui/home)	March 2023	Cholelithiasis, gallstone, gallstones and gall

HISTORY

Protocol first published: Issue 3, 2017

CONTRIBUTIONS OF AUTHORS

All authors contributed to the preparation of this review and approved the final version.

AMM and AC contributed subject expertise.

AMM and DT contributed systematic review expertise.

NS contributed statistical expertise.

DECLARATIONS OF INTEREST

AMM: none.

NS: none.

AC: none.

DT is an editor with the Cochrane Injuries Group.

SOURCES OF SUPPORT

Internal sources

- University of Hertfordshire, UK

  Access to electronic resources including peer-reviewed journals.

External sources

- The Cochrane Hepato-Biliary Group Editorial Team, Denmark

  Provided guidance to authors and ran the peer review process.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review differs from the previously published protocol (Madden 2021) by addressing updated Cochrane requirements including MECIR (Higgins 2021d) and use of Cochrane's RoB 2 tool (Sterne 2019).

We searched the EU Clinical Trials Register (www.clinicaltrialsregister.eu) instead of the European Medicines Agency.

We did not search the Food and Drug Administration website as their trials are now registered on ClinicalTrials.gov.

We searched for grey literature in the System for Information on Grey Literature in Europe OpenGrey (www.opengrey.eu), which is archived (easy.dans.knaw.nl/ui/home).

We expanded the gallstone diagnosis from ultrasound as described in the protocol to include radiolucent or other conclusive imaging methods (i.e. X-ray, oral cholecystography, or magnetic resonance imaging) due to the number of studies that were undertaken before ultrasound was widely available.

We included only data from trials that reported at least one of the defined primary and secondary outcomes of the systematic review due to the number of older studies which did not report their primary or secondary outcomes but did report multiple laboratory results that were not relevant to the primary or secondary outcomes of the systematic review.

We removed two secondary outcomes listed in the protocol because they were ambiguous and considered to be included in the primary outcome of proportion of participants with serious adverse events. The text deleted was "Proportion of participants admitted to hospital for gallstone-related complications, at longest follow-up" and "Proportion of participants subjected to a surgical intervention, at longest follow-up".

We extracted categorical data presented graphically on complete, partial, non-dissolution of gallstones, and dropouts from the frequencies given in the bar charts for each of the four outcomes by dietary intervention (Lefkof 1986). We re-analysed data using Fisher's exact test chosen in preference to the Chi^2 test because the expected number of participants in some categories was fewer than five.

We used the RoB 2 tool in Microsoft Word to store the data in place of using Microsoft Excel.

We specified the population in the title, so now it reads: "Modified dietary fat intake for treatment of gallstone disease in people of any age."