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Malhotra A, Shafiq N, Arora A, Singh M, Kumar R, Malhotra S

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[Intervention Review]

Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia

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ABSTRACT

Background

A cholesterol-lowering diet and several other dietary interventions have been suggested as a management approach either independently or as an adjuvant to drug therapy in children and adults with familial hypercholesterolaemia (FH). However, a consensus has yet to be reached on the most appropriate dietary treatment. Plant sterols are commonly used in FH although patients may know them by other names like phytosterols or stanols.

Objectives

To examine whether a cholesterol-lowering diet is more effective in reducing ischaemic heart disease and lowering cholesterol than no dietary intervention in children and adults with familial hypercholesterolaemia. Further, to compare the efficacy of supplementing a cholesterol-lowering diet with either omega-3 fatty acids, soya proteins, plant sterols or plant stanols.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Inborn Errors of Metabolism Trials Register, which is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of *The Cochrane Library*), quarterly searches of MEDLINE and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease.* Most recent search of the Group's Inborn Errors of Metabolism Trials Register: 22 August 2013. We also searched PubMed to 05 February 2012.

Selection criteria

Randomised controlled trials, both published and unpublished, where a cholesterol-lowering diet in children and adults with familial hypercholesterolaemia has been compared to other forms of dietary treatment or to no dietary intervention were included.

Data collection and analysis

Two authors independently assessed the trial eligibility and risk of bias and one extracted the data, with independent verification of data extraction by a colleague.

Main results

In the 2014 update of the review, 15 trials have been included, with a total of 453 participants across seven comparison groups. The included trials had either a low or unclear risk of bias for most of the parameters used for risk assessment. Only short-term outcomes could be assessed due to the short duration of follow up in the included trials. None of the primary outcomes, (incidence of ischaemic heart disease, number of deaths and age at death) were evaluated in any of the included trials. No significant differences were noted for the majority of secondary outcomes for any of the planned comparisons. However, a significant difference was found for the following comparisons and outcomes: for the comparison between plant sterols and cholesterol-lowering diet (in favour of plant sterols), total cholesterol levels, mean difference 0.30 mmol/l (95% confidence interval 0.12 to 0.48); decreased serum LDL cholesterol, mean difference -0.60 mmol/l (95% CI -0.89 to -0.31). Fasting serum HDL cholesterol levels were elevated, mean difference -0.04 mmol/l (95% CI -0.11 to 0.03) and serum triglyceride concentration was reduced, mean difference -0.03 mmol/l (95% CI -0.15 to -0.09), although these changes were not statistically significant. Similarly, guar gum when given as an add on therapy to bezafibrate reduced total cholesterol and LDL levels as compared to bezafibrate alone.

Authors' conclusions

No conclusions can be made about the effectiveness of a cholesterol-lowering diet, or any of the other dietary interventions suggested for familial hypercholesterolaemia, for the primary outcomes: evidence and incidence of ischaemic heart disease, number of deaths and age at death,due to the lack of data on these. Large, parallel, randomised controlled trials are needed to investigate the effectiveness of a cholesterol-lowering diet and the addition of omega-3 fatty acids, plant sterols or stanols, soya protein, dietary fibers to a cholesterol-lowering diet.

PLAIN LANGUAGE SUMMARY

Dietary modifications for managing familial hypercholesterolaemia

Familial hypercholesterolaemia is an inherited disorder characterised by a raised blood cholesterol, and premature ischaemic heart disease. Changing diet is an important management option to reduce low-density lipoprotein cholesterol (the bad cholesterol) levels. Recently, certain lipid-lowering drugs have shown to be safe and effective for the treatment of children with familial hypercholesterolaemia. However, dietary management remains important either on its own or combined with drug therapy. Several strategies are used to modify diet. This review aimed to compare cholesterol-lowering dietary interventions either in combination with each other or alone. These interventions included adding omega-3 fatty acids or plant sterols or plant stanols or soya proteins to diet. Fifteen trials were included in this updated review. The included trials had either a low or unclear risk of bias for most of the domains used for risk assessment. All the trials were short term and the majority were cross-over in design. For most of the comparisons there was no significant difference in the various intervention strategies when compared to cholesterol-lowering diet. However, for total cholesterol levels, serum low density lipoprotein (LDL) concentrations, a significant benefit was obtained with plant sterols. However, before drawing any conclusions, methodological problems with pooling results from cross-over trials should be considered. There is a need for long-term trials with parallel group design to assess the potential benefits and harms of a cholesterol-lowering diet.

BACKGROUND

Description of the condition

Familial hypercholesterolaemias are a group of genetic disorders causing severe elevations of blood cholesterol levels. Total cholesterol concentrations in heterozygous familial hypercholesterolemia (FH) patients are in the range of 9 to 14.2 mmol/l (350 to 550 mg/dL) and in homozygotes range from 16.8 to 25.9 mmol/l (650 to 1000 mg/dL) (Goldberg 2011; SBRG 1991). This disorder is one of the most common congenital metabolic disorders; the prevalence of heterozygous FH is approximately 1 in 300 to 500 with much higher incidence in certain populations, such as the Afrikaners, Christian Lebanese, Finns, and French-Canadians (Marais 2004). The characteristic features of FH include elevated levels of low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) in the circulation, deposits of cholesterol in peripheral tissues, presence of tendon xanthomas and accelerated atherosclerosis, leading to premature cardiovascular events (Goldstein 1995). Primary mutations causing FH are either due to defects in the low density lipoprotein-receptor gene (LDLR), apolipoprotein B-100 gene (APOB), or proprotein convertase subtilisin/kexin type 9 gene (PCSK9), singly or in combination (Rader 2003). The most prevalent of these genetic defects are defects in the LDLR gene with approximately 1600 known (till date) mutations in the LDLR gene causing almost 85% to 90% cases of FH. Defects in the APOB gene account for 5% to 10% of FH in northern European population (less in other populations). The PCSK9 gene defects account for about 5% of cases of FH (Hopkins 2011).The most severe form is related to total lack of receptors (receptor-negative mutations), while 'receptor-defective' mutations that comprise most of the mutations are usually accompanied by lesser symptoms (Austin 2004).

It is recommended that in children under 16 years of age, diagnosis of FH is based on a total cholesterol level of above 6.7 mmol/l (260 mg/dl) and a LDL cholesterol of above 4.0 mmol/l (155 mg/dl) on two measurements taken one month apart (Wray 1996). In the 1994 revision of the Simon Broome Register Group definition, cases are categorised as 'definite' or 'possible' (Marks 2003). According to the revision, 'DNA based evidence of an LDL-receptor mutation or familial defective apoB-100' was added as a sufficient criteria for 'definite' familial hypercholesterolaemia diagnosis. The aim of treatment in children and adults is the reduction of blood LDL cholesterol concentrations in order to reduce the risk of ischaemic heart disease.

Management of FH aims at lowering LDL by ≥ 50% or to < 3.36 mmol/l (130mg/dL). Statins are the most preferred pharmacological agents recommended for the treatment of FH along with diet and physical activity management in all age groups (Avis 2007; Shafiq 2007). Four statins (lovastatin, simvastatin, pravastatin and atorvastatin) have also been approved by U.S. Food and Drug Administration (US FDA) for use in children with familial hypercholesterolaemia. Children who do not achieve the LDL cholesterol goal after prescribed initial statin dosing need higher dose of statin or addition of another lipid lowering agent. Ezetimibe, a cholesterol absorption inhibitor, is recommended as a monotherapy or in combination with statins in children and adolescents (Yeste 2009). Bile acid sequestrants cholestyramine and cholestipol are not recommended for use in pediatric age group due to severe gastrointestinal side effects and poor palatability. Colesvelam, another bile acid sequastrant, can be used in boys aged 7 to 10 years and in postmenarchal girls as monotherapy or as adjuvant to statins. Niacin and fibrates are not recommended in the pediatric age group due to their adverse effects (O'Connor 1990; Tonstad 1997a).

Description of the intervention

A cholesterol-lowering diet based on the following principles is recommended in the United Kingdom, the USA and elsewhere for the dietary treatment of FH (Maclean 1994; Goldstein 1995; AHA Statement 2007):

1. reduction in the intake of saturated fatty acids (fatty acids are components of fats);
2. reduction in dietary cholesterol intake;
3. reduction in total fat intake;
4. manipulation of carbohydrate intake to replace the energy deficit of the low fat diet;
5. increasing the intake of certain dietary components, e.g. garlic, onions, soy protein, plant sterols and stanols and omega-3 (ω-3) fatty acids, barley, psyllium, oat bran and rice bran.

How the intervention might work

The currently prescribed diet is sometimes considered to be monotonous and can lead to problems with compliance. The reduction in fat intake, if taken to the extreme, could potentially lead to a deficiency of essential fatty acids and fat soluble vitamins and a reduction in the overall energy content of the diet which has implications for satiety and growth in children who have relatively high energy requirements. An increase in the carbohydrate content of the diet may lead to raised blood levels of another type of fat, called triglyceride, which is also a risk factor for ischaemic heart disease. In addition, the aim of the diet is to decrease the total cholesterol concentration in the blood. However this form of dietary treatment may result in not only a reduction of LDL cholesterol but also high density lipoprotein (HDL) levels (Howell 1997). HDL is thought be involved in the removal of cholesterol from the blood and therefore any intervention which lowers the levels of HDL in the blood could have a detrimental effect. In view of this, a number of other dietary therapies have been considered for the treatment of FH, including:

1. manipulation of different types of fatty acids whilst maintaining normal total fat intake;
2. increasing dietary intake of soluble fibre;
3. increasing the dietary intake of antioxidants;
4. increasing the intake of certain dietary components, e.g. garlic, onions, soy protein, plant sterols and stanols and omega-3 (ω-3) fatty acids (AHA Statement 2007).

Several scientific and authoritative bodies recommend the daily consumption of 2 g plant stanols or plant sterols for improving blood lipid levels (US FDA 2010). Phytosterols, found in fat-soluble fractions of plants, chemically resemble cholesterol and inhibit cholesterol absorption in the small intestine. They reduce plasma total and LDL-C levels (Nigon 2001).

Oral omega-3 ethyl esters improve the lipid profile principally by reducing TG levels. However, changes in TC and HDL-C were generally not found to be clinically significant, with a small net

increase in LDL-C associated with a shift toward less atherogenic LDL subfractions (Levantesi 2010)

β-glucan contained in soy protein has been shown to slow gastric emptying, digestion, and absorption (Schneeman 1998). This causes increased excretion of bile acids and neutral sterols, increasing catabolism of cholesterol, and reduced absorption of cholesterol and fat (Marlett 1997).

Various soluble fibers reduce total and LDL Cholesterol as has been previously shown (Brown 1999). However, this effect was only modest. The lipid lowering effects of soluble dietary fibers acts through its ability to increase intraluminal viscosity thereby affecting the entero-hepatic recirculation ob bile acids and lipid metabolism.

Why it is important to do this review

The majority of these interventions do not appear to have been adequately assessed and consensus has yet to be reached on the most appropriate dietary treatment for FH. The aim of this review was to assess the effectiveness of the currently recommended cholesterol lowering diet compared to no dietary treatment or to other forms of dietary intervention.

OBJECTIVES

The aims of this review were to examine in children and adults with familial hypercholesterolaemia.

1. Whether manipulating the fat, protein or carbohydrate content of the diet influences serum lipid levels and the risk of ischaemic heart disease;
2. What effect does adding ω-3 fatty acids (or their ethyl esters) to the background diet have on serum lipid levels and the risk of ischaemic heart disease?
3. What effect does adding plant sterols or stanols (both usually given in the form of esters) to the background diet have on serum lipid levels and the risk of ischaemic heart disease? Is there any dose response effect?
4. Does adding soy protein to the background diet influence serum lipid levels and the incidence of ischaemic heart disease?
5. Does adding dietary fibers such as barley, oat bran, rice bran , flax seeds or psyllium influence serum lipid levels and the incidence of ischemic heart disease?
6. Does using any of the above dietary strategies in addition to lipid lowering drugs have any added benefit?

Post hoc change:these comparisons in the current update have been changed from the previous review, in lieu with the growing knowledge about the effects of dietary supplements in altering blood lipid levels.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), both published and unpublished. Trials where quasi-randomisation methods such as alternation were included if there was sufficient evidence that the treatment and comparison groups were comparable in terms of clinical and nutritional status.

Types of participants

Children and adults with familial hypercholesterolaemia. Trials which included people with familial hypercholesterolaemia alongside those with non-familial hypercholesterolaemia were only included if the group of familial individuals was well defined and the results for this group were available.

Types of interventions

Cholesterol-lowering diet or any other dietary intervention intended to lower serum total and LDL cholesterol, for a period of at least six months. When dietary treatment had been used as a control in a trial of cholesterol-lowering drugs, these trials were excluded. However, trials were included in the review when the only difference between the control and treatment groups was the diet, for example, if a drug treatment alone was compared to the same drug treatment in combination with dietary treatment. Trials where one form of modified dietary intake was compared to another form of dietary intake were included if the comparison was done in a head-to-head comparison.

Types of outcome measures

Primary outcomes

1. Evidence and incidence of ischaemic heart disease
2. Number of deaths
3. Age at death

Secondary outcomes

1. Fasting serum total cholesterol concentration
2. Fasting serum LDL cholesterol
3. Fasting serum HDL cholesterol
4. Fasting serum triglyceride concentration
5. Fasting apolipoprotein A-1concentration,
6. Fasting apolipoprotein B-100 concentration
7. Quality of life
8. Compliance
9. Morbidity
10. Weight, height and other measures of nutritional status
11. Micronutrient intake

Search methods for identification of studies

Electronic searches

Relevant trials were identified by searching the Inborn Errors of Metabolism Trials Register using the term: diet*.

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease.* Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Register: 22 August 2013.

An additional search of of the Cochrane Central Register of Controlled Trials (CENTRAL) was undertaken (05 March 2012) (Appendix 1).

Searching other resources

Clinicaltrials.gov (www.clinicaltrials.gov) was also searched. Five trials were identified, none of them was completed and the recruitment status was unknown .

Additional trials were identified from handsearching the *Journal of Inherited Metabolic Disease* (from inception (1978) to 5 March 2012).

Additional trials were identified from the reference lists of identified trials. Unpublished work was identified through the searching of the abstract books of the major conference on inborn errors of metabolism and metabolic disease.

Data collection and analysis

Selection of studies

At initial review stage and for each update, two authors independently selected the trials to be included in the review.

Data extraction and management

Two review authors (AR and AM) independently extracted data using a pre-designed data extraction form that contained publication details, patient population, randomisation, allocation concealment, details of blinding measures, description of interventions and results (Zavala 2006). They resolved any differences in the extracted data by consulting the other review authors (NS, SM and MS). The data entered into Review Manager software (RevMan 5.1) for was rechecked for accuracy (RevMan 2011).

Due to the diverse range of dietary interventions suggested for FH, the authors divided the trials into the following comparisons - cholesterol lowering diet with no intervention; ω-3 fatty acids added to cholesterol lowering diet with cholesterol lowering diet alone; plant sterols added to cholesterol lowering diet with cholesterol lowering diet alone; plant stanols added to cholesterol lowering diet with cholesterol lowering diet alone; soya protein added to cholesterol lowering diet with cholesterol lowering diet alone; barley added to cholesterol lowering diet with cholesterol lowering diet alone; and dietary modification with lipid lowering drugs; and lipid lowering drugs alone.

The authors planned to group outcome data into those measured at up to one, three, six and twelve months and annually thereafter. However, as was the case, if outcome data were recorded at other time periods (e.g. one- to two-month data) then the authors planned to consider examining these as well. Between a fortnight and one month is generally the time when the treatment effects of dietary intervention on lipids become visible. In order to see how the effects are maintained, analyses at longer periods are desirable. For the primary outcomes, analysing the results of longer follow-up is necessary. For outcomes relating to weight, it may not be apparent in the trials whether an increase or decrease in weight would be desirable. For example, in a group of overweight adults with FH, a reduction in body weight may be desirable. However, for adults of normal body weight, such a reduction may not be desirable. Therefore, unless a judgement can be made on whether it is desirable for weight to increase, decrease or remain static during a trial, the authors planned to discuss data on body weight and related outcomes in the results section of the review, but not include these in the meta-analysis.

Assessment of risk of bias in included studies

The authors independently assessed the following domains as either low, unclear or high risk of bias:

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data addressed;
5. free of selective outcome reporting;
6. free of other bias.

Overall, trials were considered at high-risk of bias if we could only assess the majority of domains as having a high or unclear risk. The authors resolved any differences by consultation.

Measures of treatment effect

For future updates of the review, if we have data for the two primary outcomes of incidence of ischaemic heart disease and death, the number of events and the total number randomised in each group will be taken to calculate the odds ratio and 95% confidence intervals (CIs).

We analysed continuous outcomes using the mean difference (MD) and associated 95% CIs. For future updates, we will calculate the standardised mean difference (SMD) if different scales of measurement have been used. When only the standard error (SE) was provided, we converted this to the SD by multiplying the SE by the square root of the number of participants.

Unit of analysis issues

Where we obtained data from cross-over trials, we would have undertaken a paired analysis if possible, to allow a within-individual comparison of the treatment intervention. This is the preferred method of analysis of data from cross-over trials (Elbourne 2002). As these data were not available from any of the trials included in the review, we used data from the first arm of two of the trials in the analysis (Laurin 1991; Wolfe 1992). For the remaining trials, data presented in the original papers were combined from both treatments and control arms of the trials, thereby ignoring the cross-over design. We included such data in the meta-analysis, which may be considered to be justified but unsatisfactory. This should be taken into account when considering the results of this review. We attempted to contact the authors but no response was obtained.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors would have sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Data for the Guardamagna trial have not been included in the present analysis since the authors have not reported the results of subgroup of patients with familial hypercholesterolaemia (Guardamagna 2011a). The authors were requested to supply these data through electronic communication. At the time of writing this review, these data have not been received.

Assessment of heterogeneity

We tested for heterogeneity between trial results using a standard chi-square test, P < 0.1 was considered statistically significant.

We also used the I^2 statistic as a measure of heterogeneity (Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. We used the following ranges and descriptions:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

The authors planned to assess publication bias with the means of a funnel plot. The primary outcome measure was to be the main outcome for generation of the funnel plot. In the absence of an adequate number of trials reporting the primary outcome, any secondary outcome for which three or more trials were available, would have been used for funnel plot construction.

The authors intended to assess outcome reporting bias ideally by comparing the original trial protocols with the final published papers. If the protocols were not available the authors planned to compare the outcomes that were described as being measured in the 'Methods' section of the final papers with the 'Results' section to identify any outcomes that were not reported. In addition, the authors clinical knowledge would help them identify any outcomes they would normally expect to be measured, but which were not reported.

Data synthesis

We performed a fixed-effect meta-analysis where we observed no statistically significant heterogeneity. Otherwise, we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

Where heterogeneity did exist between the trials (P < 0.1 (chi-square test) or substantial to considerable heterogeneity as defined by values of I^2 above, was used as evidence of statistical heterogeneity), we investigated this and performed a random-effects meta-analysis.

We planned to undertake a subgroup analysis on those trials carried out in children.

Sensitivity analysis

We planned to perform a sensitivity analysis based on the risk of bias of the trials, including and excluding quasi-randomised trials; however, we identified insufficient trials to allow such analysis.

RESULTS

Description of studies

Results of the search

In a previous version of this review 377 references were identified from the electronic and manual search strategies. In this updated version of the review, we detected 397 references. We identified and retrieved 17 new and potentially relevant trials, of which 13 were excluded as they did not meet our inclusion criteria (*see* Characteristics of excluded studies), therefore, there are now a total of 375 excluded studies. For this update, four new trials were included (Guardamagna 2011a; Ketomäki 2004a; Nigon 2001; Wirth 1982), bringing the total number of included trials to 15.

A further two studies are listed as 'Studies awaiting classification' (Fuentes 2008; Stein 2007). We identified one ongoing study (Párraga ongoing).

Included studies

In total, 15 trials met the criteria for inclusion in the review with a total of 453 participants (Amundsen 2002; Balestrieri 1996; Chisholm 1992; Engler 2004; Guardamagna 2011a; Gylling 1995; Ketomäki 2003; Ketomäki 2004a; Ketomäki 2005; Laurin 1991; Neil 2001; Nigon 2001; O'Neill 2004; Wolfe 1992;Wirth 1982). None of the included trials reported data on the primary outcomes of this review. Long-term data were not available for any of the outcomes. After consultation with experts in the field of FH, it was decided to include short-term trials as information on change in serum lipid levels; nutritional status and nutritional intake from such trials could be considered useful.

We report on ten different interventions separately.

01 Cholesterol-lowering diet compared with no dietary intervention or nutritional advice

We included two trials in this intervention (Chisholm 1992; Guardamagna 2011a). The first of which was conducted in adults with FH (Chisholm 1992). The trial was a short-term randomised controlled cross-over trial in 19 patients with three eight-week treatment periods in each arm (high-fat diet followed by low-fat diet followed by high-fat diet compared to low-fat diet followed by high-fat diet followed by low-fat diet). All participants continued with lipid-lowering medication (simvastatin) throughout the trial. In the second trial 40 children were randomised to receive either cholesterol lowering diet comprising of yeast rice extract, monacolins, policosanaols, folic acid coenzyme Q10, astaxanthin or placebo (Guardamagna 2011a). Patients either had familial hypercholesterolemia (n = 24) or combined familial hyperlipidaemia (n = 16). No results from this trial could be included in the review as no subgroup analysis for patients with FH was undertaken separately.

02 Supplementation with omega-3 fatty acids given with a cholesterol-lowering diet compared to a cholesterol-lowering diet alone

Two trials assessed the effect of adding ω-3 fatty acids to a cholesterol-lowering diet (Balestrieri 1996; Engler 2004). The Balestrieri trial assessed the impact of increasing the intake of fish oils in adults (n = 16) with FH (Balestrieri 1996). The Engler trial investigated the effect of docosahexaenoic acid (DHA)

supplementation to a cholesterol-lowering diet in children with FH (n = 20) (Engler 2004). Both trials were of cross-over design, of short duration and provided data which we were able to include in a meta-analysis.

03 Cholesterol-lowering diet compared with dietary interventions to increase intake of plant stanols

We included two cross-over trials, one of which reported on children with FH (Gylling 1995) and one on adults (Ketomäki 2004a). The Gylling trial (n = 14), which was a short-term trial, evaluated the effect of sitostanol (3 g/day) ester dissolved in rapeseed oil-rich margarine for six weeks in a double-blind cross-over design (Gylling 1995). The Ketomaki trial (n = 5) studied the effect of both plant stanol and sterol ester spreads on triglyceride-rich lipoprotien (TRL) removal in statin-treated patients with FH using intravenous intralipid-squalene fat tolerance test (Ketomäki 2004a).

04 Cholesterol-lowering diet compared with dietary interventions to increase intake of plant sterols

For this comparison, five trials have been included (Amundsen 2002; Guardamagna 2011a; Ketomäki 2004a; Neil 2001; Nigon 2001). Three of the trials were on adults (Ketomäki 2004a; Neil 2001; Nigon 2001) and two on children (Amundsen 2002; Guardamagna 2011a). All five trials were cross-over in design. The Neil trial presented data on the trials FH subgroup (n = 30) (type IIa patients were also included (n = 26)) as a parallel group (Neil 2001). All five trials were short-term with each arm of the trial lasting between one and two months (with variable washout periods).

The Amundsen (n = 41), Neil and Nigon (n = 53) trials compared a plant sterol-enriched fat spread with a control fat spread not enriched with plant sterols (Amundsen 2002; Neil 2001; Nigon 2001). The Ketomaki trial (n = 5) compared low fat plant sterol ester spread or low fat plant stanol ester spread over and above ongoing drug therapy (Ketomäki 2004a). The Guardamagna trial (n = 24) compared a dietary supplement containing 200 mg red yeast rice extract, corresponding to 3 mg of monacolins, and 10 mg policosanols once-daily versus placebo (Guardamagna 2011a).

05 Soy protein as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment

No trials were identified.

06 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment

The dietary fibers which were considered were barley, guar gum, psyllium, oat bran, flax seed and rice bran. Only one trial (n = 12) was found which satisfied inclusion criteria (Wirth 1982). In this trial guar gum was administered with bezafibrate and this was compared with bezafibrate given alone. The trial included adult patients with familial hypercholesterolemia.

07 Dietary modification with lipid-lowering drugs

No trials were identified.

08 Lipid-lowering drugs alone

No trials were identified.

09 Cholesterol-lowering diet compared to a high-protein diet

We were able to include two cross-over trials for this intervention (Laurin 1991; Wolfe 1992). One trial assessed the effect of soy products in children (n = 10) with FH (Laurin 1991), while the other assessed the effect of a high-protein diet in adults with FH (n = 5) (Wolfe 1992). Both were short-term trials with each arm of the trial lasting between one and three months.

10 Comparing one form of dietary intervention with another, where cholesterol-lowering diet is not the control group

Three short-term trials of adults with FH were included in this intervention group (Ketomäki 2003; Ketomäki 2005; O'Neill 2004). In the 2005 Ketomaki trial, adults with FH (n = 18) receiving hypolipidaemic drugs were randomised to receive either plant sterols or stanols. The trial was of cross-over design and did not allow the comparison of the addition of plant sterols or stanols supplementation to drug treatment (Ketomäki 2005). In another trial by Ketomaki, 16 out of 23 children had FH (Ketomäki 2003). The data from these children were not reported separately and the authors were contacted for this information. This trial compared plant sterol and sterol ester spreads added to low-fat diet given to all the participants. The third trial was of parallel design with three separate treatment groups: plant sterols versus low-dose plant stanols versus high-dose plant stanols (O'Neill 2004). This trial had 69 FH participants who were included alongside unaffected individuals (O'Neill 2004). The authors did provide the data for the 69 individuals with FH. However, these data were not in the format which could be used for analysis; percentage change in the lipid levels were given instead of actual values.

Excluded studies

There were over 300 studies excluded for the following reasons: not being an RCT; not being trials of dietary interventions; not including participants with FH; and including familial participants alongside non-familial participants but not as a well-defined subgroup.

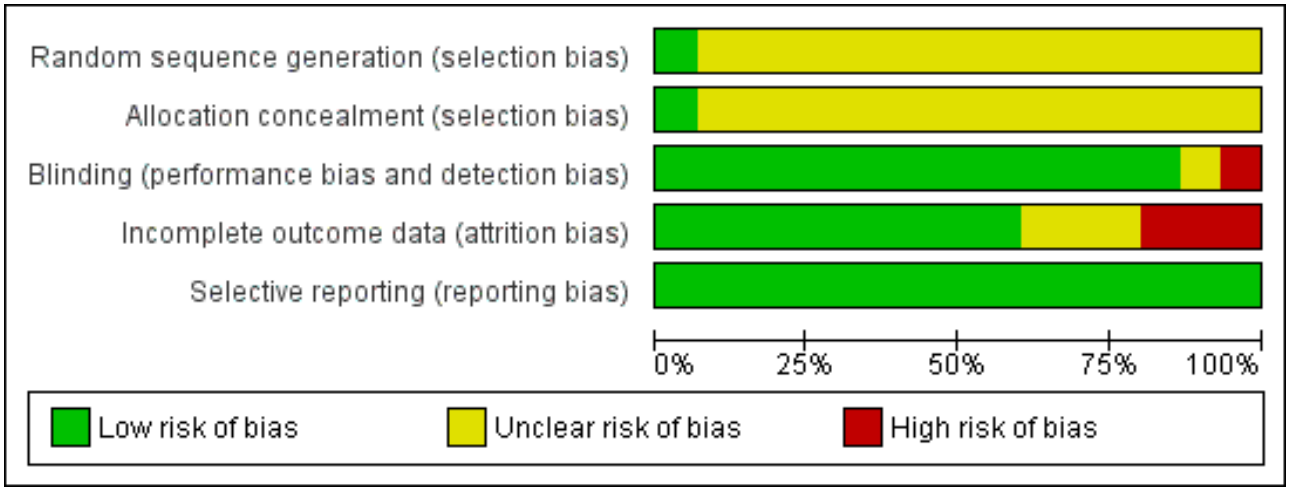
Studies awaiting classification

In addition two studies were classified as studies awaiting classification for reasons that include non-availability of required data or inadequacy of dietary intervention (Fuentes 2008; Stein 2007).

Risk of bias in included studies

Please refer to the additional figure for a summary of the risk of bias (Figure 1).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Generation of the randomisation sequence was adequate in one (low risk of bias), where authors have stated that computer-generated random numbers were used to assign the participants to either test or the control group with equal probability (Neil 2001) and unclear in the remaining 13 trials.

Concealment of allocation was adequate in one trial (low risk of bias) where the trial reports have described the methods adopted for assuring allocation concealment (Neil 2001). Tamper-proof block randomisation was used and clinic and lab staff remained unaware of the assigned treatment throughout the trial. However, concealment of allocation was unclear for the remainder of the trials (unclear risk of bias) (Amundsen 2002; Balestrieri 1996; Chisholm 1992; Engler 2004; Guardamagna 2011a; Gylling 1995; Ketomäki 2003; Ketomäki 2004a; Ketomäki 2005; Laurin 1991; O'Neill 2004; Wolfe 1992; Wirth 1982).

Blinding

Twelve trials were reported as being double-blinded (Amundsen 2002; Balestrieri 1996; Engler 2004; Guardamagna 2011a; Gylling 1995; Ketomäki 2003; Ketomäki 2004a; Ketomäki 2005; Laurin 1991; Neil 2001; Nigon 2001; O'Neill 2004). Information regarding blinding was not given in the other trials (Chisholm 1992; Laurin 1991; Wirth 1982). Assessment bias could therefore not be ruled out for these trials.

Incomplete outcome data

It was unclear if an intention-to-treat analysis was carried out in one of the trials, giving an unclear risk of bias (Chisholm 1992). In eight trials intention-to-treat analysis was considered adequate giving a low risk of bias (Engler 2004; Gylling 1995; Ketomäki 2003; Ketomäki 2005; Neil 2001; Wolfe 1992; Ketomäki 2004a; Nigon 2001); and in three trials participants were withdrawn from the trials and not included in the final analysis, therefore intention-to-treat analysis was not applied (Amundsen 2002; Balestrieri 1996; Laurin 1991). Two participants withdrew from one trial due to medical reasons (one suffered a heart attack and one required vascular surgery) (Balestrieri 1996). Two participants were withdrawn from another trial for lack of compliance and elevated serum lipid levels (Laurin 1991). Two trials undertook a *per protocol* analysis (Guardamagna 2011a; O'Neill 2004). In the former, six of them discontinued the trial before visit 1: two had difficulties in drinking the yogurt; two had poor adherence to the diet program; one was unable to attend visits and only one reported recurrent abdominal discomfort. No sample attrition occurred in the Wirth trial (Wirth 1982).

Selective reporting

Selective reporting was not noted in any of the include trials (Amundsen 2002; Balestrieri 1996; Chisholm 1992; Engler 2004; Guardamagna 2011a; Gylling 1995; Ketomäki 2003; Ketomäki 2004a; Ketomäki 2005; Laurin 1991; Neil 2001; Nigon 2001; O'Neill 2004; Wirth 1982; Wolfe 1992).

Effects of interventions

All the trials from which data were extracted and included in the meta-analysis employed a cross-over design except one which was a parallel trial (O'Neill 2004). Only seven of the trials presented data in such a way that the preferred method of analysis could be conducted (Engler 2004; Ketomäki 2004a; Laurin 1991; Neil 2001; Nigon 2001; O'Neill 2004; Wolfe 1992). However, such data were not provided for all of the outcomes assessed in these trials. Re-analysis of the data will be undertaken at a future date if we are successful in contacting the authors for individual patient data.

Only those comparison groups for which there are eligible trials are listed below.

Only short-term outcomes are included in this review due to the length of the trials identified from the searches. For primary outcomes, incidence of ischaemic or atheromatous disease and deaths were not reported on in any of the included trials. For secondary outcomes, quality of life, compliance with treatment and morbidity were not assessed in any of the included trials. Therefore we have not listed these outcomes below.

Comparison 01: Cholesterol-lowering diet compared with no dietary intervention or nutritional advice

Two trials were identified (Chisholm 1992; Guardamagna 2011a). In the first trial which included 19 participants (Chisholm 1992). No

significant differences were found between the two interventions for any of the outcomes assessed in which data could be entered into the meta-analysis. None of the results from the second trial could be included in the meta-analysis since no subgroup analysis for patients with familial hypercholesterolemia was undertaken separately from those individuals with combined familial hyperlipidaemia (Guardamagna 2011a).

Primary outcomes

The primary outcomes of ischaemic heart disease, number of deaths and or age at death were not reported in the included trial (Chisholm 1992).

Secondary outcomes

1. Serum total cholesterol concentration (fasting)

There was no significant difference between treatments for this outcome, MD -0.40 (95% CI -0.95 to 0.15) mmol/l (Analysis 1.1) (Chisholm 1992).

2. Serum LDL cholesterol (fasting)

There was no significant difference between treatments for his outcome, MD -0.27 (95% CI -0.79 to 0.25) mmol/l (Analysis 1.2) (Chisholm 1992).

3. Serum HDL cholesterol (fasting)

There was no significant difference between treatments for his outcome, MD -0.11 (95% CI -0.34 to 0.12)mmol/l (Analysis 1.3) (Chisholm 1992).

4. Serum triglyceride concentration (fasting)

There was no significant difference between treatments for his outcome, MD 0.06 (95% CI -0.43 to 0.55) mmol/l (Analysis 1.4) (Chisholm 1992).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting)

There was a significant difference in favouring the cholesterol-lowering diet, MD -0.06 (95% CI -0.12 to -0.01) g/L (Analysis 1.5) (Chisholm 1992).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting)

There was no significant difference in favouring the cholesterol-lowering diet, MD -0.01 (95% CI -0.05 to 0.03) g/L (Analysis 1.6) (Chisholm 1992).

7. Quality of life

This outcome was not reported in the included trial (Chisholm 1992).

8. Compliance

This outcome was not reported in the included trial (Chisholm 1992).

9. Morbidity

This outcome was not reported in the included trial (Chisholm 1992).

10. Weight, height and other measures of nutritional status

Insufficient data (weight, height, body mass index (BMI)) were provided to allow inclusion of these outcomes in the meta-analysis (Chisholm 1992). However, weight and BMI appeared to remain static during the two arms of the trial (mean BMI was 29.2 on the cholesterol-lowering diet and 29.3 on a free diet, although no SDs were provided).

11. Micronutrient intake

Not assessed in the included trial (Chisholm 1992).

COMPARISON 02: Supplementation with ω-3 fatty acids given with cholesterol-lowering diet compared to cholesterol-lowering diet alone

Two trials including 34 participants were identified (Balestrieri 1996; Engler 2004). No significant differences were found between the two interventions for any of the outcomes assessed.

Primary outcomes

The primary outcomes of ischaemic heart disease, number of death and or age at death were not reported in either of the trials (Balestrieri 1996; Engler 2004).The follow-up period was too short to have any effect on primary outcomes (four weeks in the Baestrieri trial and six weeks in the Engler trial).

Secondary outcomes

1. Serum total cholesterol concentration (fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD -0.06 (95% CI - 0.80 to 0.69) mmol/l (Analysis 2.1) (Balestrieri 1996; Engler 2004).

2. Serum LDL cholesterol (fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD -0.12 (95% CI -0.93 to 0.69) mmol/l (Analysis 2.2) (Balestrieri 1996; Engler 2004).

3. Serum HDL cholesterol (fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD 0.02 (95% CI -0.10 to 0.13) mmol/l (Analysis 2.3) (Balestrieri 1996; Engler 2004).

4. Serum triglyceride concentration (fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD 0.18 (95% CI -0.07 to 0.43) mmol/l (Analysis 2.4) (Balestrieri 1996; Engler 2004).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting)

This outcome was assessed by one trial (Balestrieri 1996). There was no significant difference between treatment groups, MD -0.02 (95% CI -0.35 to 0.31) g/L (Analysis 2.5).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting)

This outcome was assessed by one trial (Balestrieri 1996). There was no significant difference between treatment groups, MD 0.01 (95% CI -21.99 to 22.01 g/L (Analysis 2.6).

7. Quality of life

Neither trial reported on this outcome (Balestrieri 1996; Engler 2004).

8. Compliance

Neither trial reported on this outcome (Balestrieri 1996; Engler 2004).

9. Morbidity

Neither trial reported on this outcome (Balestrieri 1996; Engler 2004).

10. Weight, height and other measures of nutritional status

Neither trial reported on this outcome (Balestrieri 1996; Engler 2004).

11. Micronutrient intake

Neither trial reported on this outcome (Balestrieri 1996; Engler 2004).

COMPARISON 03: Cholesterol-lowering diet compared with dietary interventions to increase intake of plant stanols

Two trials were included, one on children (N = 14) (Gylling 1995) and one on adults (N = 5) (Ketomäki 2004a).

Primary outcomes

The authors did not evaluate any of the primary outcomes of ischaemic heart disease and number of deaths and or age at death in either of these trials (Gylling 1995; Ketomäki 2004a).

Secondary outcomes

1. Serum total cholesterol concentration (fasting)

There was a significant difference in cholesterol level between the stanol treatment and cholesterol-lowering diet group favouring stanol treatment, MD 0.51 (95% CI 0.07 to 0.96) mmol/l after pooling the two trials (Analysis 3.1) (Gylling 1995; Ketomäki 2004a).

2. Serum LDL cholesterol (fasting)

There was a significant difference between stanol treatment and the cholesterol-lowering diet group favouring stanol treatment, MD 0.71 (95% CI 0.43 to 0.99) mmol/l after pooling (Analysis 3.2) (Gylling 1995; Ketomäki 2004a).

3. Serum HDL cholesterol (fasting)

The difference between treatment groups after pooling did not quite reach statistical significance, MD -0.08 (95% CI -0.15 to -0.00) mmol/l (Analysis 3.3) (Gylling 1995; Ketomäki 2004a).

4. Serum triglyceride concentration (fasting)

There was no significant difference between treatment groups after pooling, SMD 0.12 (95% CI -0.52 to 0.76) mmol/l (Analysis 3.4) (Gylling 1995; Ketomäki 2004a).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting)

This was not assessed in the included trials (Gylling 1995; Ketomäki 2004a).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting)

This was not assessed in the included trials (Gylling 1995; Ketomäki 2004a).

7. Quality of life

Neither trial reported on this outcome (Gylling 1995; Ketomäki 2004a).

8. Compliance

Neither trial reported on this outcome (Gylling 1995; Ketomäki 2004a).

9. Morbidity

Neither trial reported on this outcome (Gylling 1995; Ketomäki 2004a).

10. Weight, height and other measures of nutritional status

Neither trial reported on this outcome (Gylling 1995; Ketomäki 2004a).

11. Micronutrient intake

Neither trial reported on this outcome (Gylling 1995; Ketomäki 2004a).

COMPARISON 04: Cholesterol-lowering diet compared with dietary interventions to increase intake of plant sterols

Data from four trials with 129 participants were included in this comparison (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001). A fifth trial was also eligible, but the data from the trial done by Guardamagna have not been included in the present analysis since the authors have not reported the results of subgroup of patients with familial hypercholesterolaemia (Guardamagna 2011a). The authors were requested to supply these data through electronic communication. At the time of writing this review, these data have not been received. However, in their manuscript do mention that the dietary supplementation did favourably alter the lipid profile in patients with familial hypercholesterolaemia similar to that seen in the combined analysis of all the patients.

Primary outcomes

The authors did not evaluate any of the primary outcomes of ischaemic heart disease and number of deaths and or age at death in any of the trials.

Secondary outcomes

1.Serum total cholesterol concentration (fasting)

All the four trials reported on this outcome. There was a significant difference between sterol treated participants as compared to cholesterol-lowering diet alone favour of sterol, MD 0.30 (95% CI 0.12 to 0.48) mmol/l (Analysis 4.1) (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

2. Serum LDL cholesterol (fasting)

All the four trials reported on this outcome. The LDL was significantly lower with the sterol treatment, MD -0.60 (95% CI -0.89 to -0.31) mmol/l (Analysis 4.2) (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

3. Serum HDL cholesterol (fasting)

All the four trials reported on this outcome. The HDL levels were not significantly different between plant sterol treated and cholesterol-lowering diet alone, MD -0.04 (95% CI -0.11 to 0.03) mmol/l (Analysis 4.3) (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

4. Serum triglyceride concentration (fasting)

All the four trials reported on this outcome. The TG levels were not significantly lower with sterol treatment, MD -0.03 (95% CI -0.15 to 0.09) mmol/l, although there was considerable heterogeneity (Analysis 4.4) (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting)

This outcome was assessed by two trials (Amundsen 2002; Nigon 2001). There was no significant difference between treatment groups, MD 0.03 (95% CI -0.08 to 0.14) g/L (Analysis 4.5) (Amundsen 2002; Nigon 2001).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting)

This outcome was assessed by two trials (Amundsen 2002, Nigon 2001). There was no significant difference between treatment groups, MD 0.02 (95% CI -0.09 to 0.13) g/L (Analysis 4.6).

7. Quality of life

None of the trials reported on this outcome (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

8. Compliance

None of the trials reported on this outcome (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

9. Morbidity

None of the trials reported on this outcome (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

10. Weight, height and other measures of nutritional status

None of the trials reported on this outcome (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

11. Micronutrient intake

None of the trials reported on this outcome (Amundsen 2002; Ketomäki 2004a; Neil 2001; Nigon 2001).

COMPARISON 06: Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment

One trial in adults was included (N = 12) (Wirth 1982).

Primary outcomes

The authors did not evaluate any of the primary outcomes of ischaemic heart disease and number of deaths and or age at death in any of the trials (Wirth 1982).

Secondary outcomes

1.Serum total cholesterol concentration (fasting)

There was no significant difference between guar gum and bezafibrate treated group as compared to group of patients treated with bezafibrate alone, MD -0.57 (95% CI -2.08 to 0.94) mmol (Analysis 6.1) (Wirth 1982).

2. Serum LDL cholesterol (fasting)

The LDL was significantly lower when guar gum was combined with bezafibrate compared to bezafibrate alone, MD -1.83 (95% CI -3.32 to -0.34) mmol (Analysis 6.2) (Wirth 1982).

3. Serum HDL cholesterol (fasting)

There was no change in the level of HDL in the group receiving guar gum in addition to bezafibrate, MD -0.18 (95% CI -0.46 to 0.10) mmol (Analysis 6.3) (Wirth 1982).

4. Serum triglyceride concentration (fasting)

There was no significant change in this outcome with the use of guar gum, MD -0.41 (95% CI -0.12 to 0.94) mmol (Analysis 6.4) (Wirth 1982).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting)

No significant change was noted for this outcome, MD -0.04 (95% CI -6.75 to 6.83) gm/L (Analysis 6.5) (Wirth 1982).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting)

There was a significant change noted for this outcome in favour of the use of guar gum with bezafibrate, MD -0.50 (95% CI -0.65 to -0.35) gm/L (Analysis 6.6) (Wirth 1982).

7. Quality of life

This outcome was not reported in the included trial (Wirth 1982).

8. Compliance

The trial reported that none of the patients were excluded for inadequate compliance (Wirth 1982).

9. Morbidity

This was not reported in the included trial (Wirth 1982).

10. Weight, height and other measures of nutritional status

Only weight was reported in the trial. There was no significant difference in the weights in the two groups at the end of the trial period, MD -0.40 (95% CI -5.09 to 5.89) gm/L (Analysis 6.7) (Wirth 1982).

11. Micronutrient intake

This was not evaluated in the included trial (Wirth 1982).

COMPARISON 09: Cholesterol-lowering diet compared to a high-protein diet

Two trials were included in this comparison (Laurin 1991; Wolfe 1992). One of a cholesterol-lowering diet compared with a high-protein diet (five participants) (Wolfe 1992) and one of a cholesterol-lowering diet compared with a soy-protein diet (10 participants)

(Laurin 1991). No significant differences were found between the two interventions for any of the outcomes assessed.

Primary outcomes

The authors did not evaluate any of the primary outcomes of ischaemic heart disease and number of deaths and or age at death (Laurin 1991; Wolfe 1992).

Secondary outcomes

1. Serum total cholesterol concentration (fasting and non-fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD 0.08 (95% CI - 0.65 to 0.81) mmol/l (Analysis 5.1) (Laurin 1991; Wolfe 1992).

2. Serum LDL cholesterol (fasting and non-fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD 0.12 (95% CI -0.46 to 0.69) mmol/l (Analysis 5.2) (Laurin 1991; Wolfe 1992).

3. Serum HDL cholesterol (fasting and non-fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD -0.07 (95% CI -0.23 to 0.08) mmol/l (Analysis 5.3) (Laurin 1991; Wolfe 1992).

4. Serum triglyceride concentration (fasting and non-fasting)

Both trials reported on this outcome. There was no significant difference between treatment groups, MD 0.25 (95% CI -0.01 to 0.50) mmol/l (Analysis 5.4) (Laurin 1991; Wolfe 1992).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting and non-fasting)

This outcome was assessed by one trial (Laurin 1991). There was no significant difference between treatment groups, MD 0.04 (95% CI -5.84 to 5.92) g/L (Analysis 5.5) (Laurin 1991; Wolfe 1992).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting and non-fasting)

This outcome was assessed by one trial (Laurin 1991). There was no significant difference between treatment groups, MD 0.00 (95% CI -3.92 to 3.92) mg/dL (Analysis 5.6).

7. Quality of life

This outcome was not assessed in either trial (Laurin 1991; Wolfe 1992).

8. Compliance

This outcome was not assessed in either trial (Laurin 1991; Wolfe 1992).

9. Morbidity

This outcome was not assessed in either trial (Laurin 1991; Wolfe 1992).

10. Weight, height and other measures of nutritional status

These outcomes were assessed in one trial (Laurin 1991). There was no significant difference between treatment groups for any of these outcomes: weight, MD 0.00 (95% CI -7.58 to 7.58) kg (Analysis 5.7); height, MD 0.00 (95% CI -7.63 to 7.63) cm (Analysis 5.8); and BMI, MD -0.09 (95% CI -2.77 to 2.95) (Analysis 5.9). No pooling of data were possible as the results are from one trial only.

11. Micronutrient intake

This outcome was not assessed in either trial (Laurin 1991; Wolfe 1992).

COMPARISON 10: One form of dietary intervention compared to another form of dietary intervention

Three short-term trials of adults with FH were included in this intervention group (Ketomäki 2003; Ketomäki 2005; O'Neill 2004). Two trials included participants with and without FH, but data are not presented separately in either trial for the subset of participants with FH (Ketomäki 2003; O'Neill 2004).

Primary outcomes

The authors did not evaluate any of the primary outcomes of ischaemic heart disease and number of deaths and or age at death (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

Secondary outcomes

1. Serum total cholesterol concentration (fasting and non-fasting)

The results of 134 participants in the O'Neill trial demonstrated a significant reduction in serum total cholesterol (TC) from baseline at the end of two months in both the high-dose (2.6 g) stanol group (HSTA) and the low-dose (1.6 g) stanol group (LSTA) (O'Neill 2004). In the HSTA group, serum total cholesterol levels decreased from mean (SD) 6.1 (0.20) mmol/l at baseline to 5.3 (0.15) mmol/l ($P < 0.001$). This was also the case in the LSTA group after two months; serum total cholesterol levels showed a significant reduction from mean (SD) 5.8 (0.19) mmol/l at baseline to 5.5 (18.00) mmol/l ($P < 0.001$). In the sterol (STE) group (1.6 g), cholesterol levels were significantly reduced at one month from mean (SD) 5.8 (0.17) mmol (baseline) to 5.4 (0.15) mmol/l ($P < 0.001$) at one month. A subgroup analysis of the 69 FH participants was not presented.

In the second trial, the authors noted a significant reduction in total cholesterol levels following a five-week intervention period by both stanol and sterol esters (percentage change from baseline (mean (SE of the mean (SEM)) - 9 (3) and -6 (2), respectively) (Ketomäki 2003). The data for 16 participants with FH was not presented separately.

In the third trial, in the plant stanol group, the serum total cholesterol values reduced from mean (SD) 6.30 (0.24) at baseline to 5.65 (0.22) mmol/l while in STE group, TC reduced to 5.7 (0.21) mmol/l following two consecutive four-week intervention periods (Ketomäki 2005). This reduction was significant as compared to baseline values. In both the groups the participants were on statins.

2. Serum LDL cholesterol (fasting and non-fasting)

O' Neill observed a significant reduction from baseline in LDL cholesterol in all the three groups: HSTA mean (SD) 3.77 (0.18) to 3.30 (0.14) mmol/l ($P < 0.001$); LSTA mean (SD) 3.83 (0.16) to 3.54 (0.14) ($P = 0.03$); and STE mean (SD) 3.81 (0.15) to 3.63 (0.15) ($P = 0.003$) (O'Neill 2004). The data for 69 FH participants were not available.

In the earlier Ketomaki trial, a significant percentage reduction from baseline in LDL cholesterol was noted in both stanol and sterol groups, mean (SEM) -12% (3%) and -9% (3%) respectively

(Ketomäki 2003). The data were expressed only as percentage reduction. Additionally, data for 16 FH participants were not given separately.

In the later Ketomaki trial, when given in addition to statins, a significant reduction from baseline in LDL cholesterol levels was noted in both the stanol group (mean (SD) 4.50 (0.21) to 3.81 (0.18))mmol/l and the sterol group (mean (SD) 4.50 (0.21) to 3.86 (0.19) mmol/l (Ketomäki 2005).

3. Serum HDL cholesterol (fasting and non-fasting)

While O'Neill reported no statistically significant changes in HDL cholesterol levels in the LSTA and STE groups, a significant reduction in HDL cholesterol levels was noted after two months in the HSTA group (O'Neill 2004). Again, the data for 69 FH patients were not presented separately.

In the earlier Ketomaki trial, no significant difference in HDL cholesterol level was noted in any of the groups (Ketomäki 2003). In the later Ketomaki trial, when given over and above statins, sterols caused a significant increase in HDL cholesterol; from mean (SD) 1.26 (0.05) mmol/l at baseline to 1.37 (0.04) mmol/l (Ketomäki 2005).

4. Serum triglyceride concentration (fasting and non-fasting)

O'Neill demonstrated significant decrease in triglyceride levels at two months in the HSTA group (-15.0%) and no changes in the LSTA and the STE groups (O'Neill 2004).

No significant difference in triglyceride (TG) levels was observed in either the stanol or the sterol groups in the second trial (Ketomäki 2003). In the third trial, the authors concluded significant decrease in serum TG only in the sterol group from mean (SD) 1.19 (0.10) at baseline to 1.05 (0.09) following two consecutive four-week intervention periods (Ketomäki 2005).

5. Apolipoprotein A1concentration, the protein component of HDL cholesterol (fasting and non-fasting)

None of the three trials evaluated apolipoprotein A1 concentration (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

6. Apolipoprotein B-100 concentration, the protein component of LDL cholesterol (fasting and non-fasting)

O' Neill reported a significant reduction in Apo B-100 levels in the LSTA, HSTA and STE groups at two months; -6.6%, -8.5% and -5.9% respectively) (O'Neill 2004). These data were not separately presented for FH participants. The other two trials did not report this outcome (Ketomäki 2003; Ketomäki 2005).

7. Quality of life

This outcome was not assessed in any of the trials (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

8. Compliance

This outcome was not assessed in any of the trials (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

9. Morbidity

This outcome was not assessed in any of the trials (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

10. Weight, height and other measures of nutritional status

No significant reduction from baseline was noted for weight in any of the three trials (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

11. Micronutrient intake

This outcome was not evaluated in any of the trials (Ketomäki 2003; Ketomäki 2005; O'Neill 2004).

DISCUSSION

In the present update of this review, 14 trials have been included with a total of 441 participants across seven comparison groups. The sample size of included trials is a concern as inadequately-powered trials seldom lead to meaningful conclusions. Further, the majority of trials included in this review were cross-over in design. One trial which used a parallel group design included FH participants only as a subgroup (O'Neill 2004). For another trial, the authors provided the data of FH subgroup as a parallel group, although the trial had a cross-over design (Neil 2001). This does make it important that caution be exercised in interpreting the pooled results.

Only one trial was identified which assessed the effect of a cholesterol-lowering diet compared to no dietary intervention (Chisholm 1992). This is disappointing as a cholesterol-lowering diet is the recommended dietary treatment for FH. Although no significant differences have been found between the comparisons assessed, this does not mean that the diets are not effective, rather that the data available are insufficient to reach any conclusions on the efficacy of the different dietary treatments. There is a wide range of dietary treatment options that have been suggested for FH; however, for each of these options there appear to have been very few or no trials carried out.

The use of plant sterols and stanols has received renewed attention in recent years and seven trials assessing this intervention were included in the analysis (Amundsen 2002; Ketomäki 2003; Ketomäki 2004a; Ketomäki 2005; Neil 2001; Nigon 2001; O'Neill 2004). The last one of these compared sterol and stanol substitution on the background of lipid lowering drugs, mainly statins. Both the interventions significantly improved the lipid profile. However, the trial design did not allow analysis of the effect of adding plant sterols or stanols to lipid lowering drugs when compared to lipid lowering drugs given alone. There was no effect in other outcomes like apolipoproteins A and B100.

Fish oils containing omega-3 fatty acids have also been evaluated as an option for dietary intervention (Balestrieri 1996; Engler 2004). However, much needs to be clarified on this issue as regards to the optimal dose and the ratio of docosahexaenoic acid (DHA) and eicosopentanoic acid (EPA) which should be used. More trials are needed to investigate this dietary intervention strategy.

All the trials identified were short term and did not assess long-term outcomes. It is disappointing that no long-term trials were identified as long-term outcomes may be more relevant to people with familial hypercholesterolaemia and their care givers. None of the primary outcomes could be evaluated for the same reason.

Again, there is the problem of combining the results of familial hypercholesterolaemia with hypercholesterolaemia. *A priori* subgroup analysis was not planned by any of the authors

for the trials in which this problem was noted. Two of the authors provided the data for FH participants and these trials have thus been included in the present update (Neil 2001; O'Neill 2004). For one of the trials, however, the data could not be incorporated for meta-analysis as the authors did not provide the data in the required format for evaluation by RevMan (O'Neill 2004). Hopefully, in a future version of this review these data may also be included.

Further, in view of evolving approaches in the management of familial hypercholesterolaemia, we had planned to undertake additional analysis. One of the aims of the review was to assess the usefulness of cholesterol-lowering diet over and above the drug therapy (statins, bile acid sequestrants, fenofibrate and anion exchange resins). Trials designed to evaluate various dietary modifications over and above lipid-lowering drugs are needed.

Trials in which head-to-head comparisons of various dietary intervention strategies are carried out were remarkably absent with a few exceptions. In one trial, the effect of low-dose and high-dose stanol was compared to sterol esters in a head-to-head manner (O'Neill 2004). The authors noted that, despite a trend, the improvement in serum lipid profile with a high-dose stanol ester was no better than that of low-dose stanol esters. In the other trial, sterol esters were compared with stanol esters (O'Neill 2004). The authors analysed the change from baseline in the levels of total cholesterol, LDL, HDL and triglycerides. However, a comparison between sterol and stanol ester groups was not made.

The new comparisons included in this update were soluble fibers such as barley, oat bran, rice bran, guar gum, psyllium or flax seeds and soy protein as form of dietary intervention compared to another form of dietary intervention or drug or no dietary intervention. Only one trial satisfying inclusion criteria was identified. The intervention used was guar gum with bezafibrate. It was in 12 adult familial hypercholesterolemic patients. Though statistically significant reduction in total and LDL cholesterol levels were noted, the utility of this finding in the current era of statins is suspect. A meta-analysis (Brown 1999) has shown beneficial effect of soluble dietary fibers in hypercholesterolemia and thus there is a case for studying dietary fibers in an adequately powered trial.

People with FH may be more susceptible to potentially detrimental psychological and nutritional consequences of their dietary treatment. For this reason, it is disappointing to note that very few of the trials included in this review assessed measures of nutritional status and none assessed quality of life or nutritional intake.

Publication bias cannot be ruled out. A funnel plot could not be constructed as the data required were not available in sufficient quantities. We hope that with new possibilities opening up for publishing negative trials, more trials will come to the fore and possibly be included in the review.

AUTHORS' CONCLUSIONS

Implications for practice

No conclusions can be made about the short- or long-term effectiveness of the cholesterol-lowering diet.

Considering the fact that the pooled trials did not conform completely to the requirements for pooling, careful attention should be paid when implementing the conclusions for practice. Sterol treatment did significantly lower total cholesterol; however, more evidence is required in the form of large, good quality controlled trials before sterols are recommended for people with FH.

Implications for research

A large, parallel, randomised controlled trial is needed to investigate the effectiveness of the cholesterol-lowering diet and no dietary intervention. Due to the relatively small numbers of people with this condition, it is recommended that a multi-centre approach is adopted and that participants should not be recruited to small scale trials which may preclude them from being involved in larger trials. It is also important that future trials consider the long-term outcomes in addition to short-term ones. Since drug therapy , particularly statins, is the standard of care in FH, dietary intervention would need to be studied as adjuvant. In addition, as the effect of statins on hard outcomes would be large, the effect of dietary interventions on these outcomes would be very difficult to study and effect on surrogate outcomes (LDL) would be important. To assist in ensuring the appropriateness of future trials, it would be useful to involve people with FH and their carers in the design of the trial.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amundsen 2002

Methods	Randomised controlled cross-over trial.
Participants	41 children with confirmed or suspected FH (mean age 10.5 years +/- 1.7 years). Three dropped out (2 because of family problems and one because she found the amount of spread was too large
Interventions	Plant sterol-enriched fat spread (8 weeks) versus a control spread not enriched with plant sterols (8 weeks). 4-week washout period.
Outcomes	Total, LDL, HDL cholesterol, triacylglycerol, apolipoprotein A1 and B, carotenoids, retinol and alpha-tocopherol concentrations, and albumin and other blood biochemistry.
Notes	3 children were withdrawn from the trial and not followed up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants were withdrawn from the trials and not included in the final analysis. 2 girls dropped out during the trial because of family problems not related to the project, and a third because she found that the amount of spread was too large.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported.

Balestrieri 1996

Methods	Randomised controlled cross-over trial.

Balestrieri 1996 *(Continued)*

Participants	16 participants (7 females, 9 males) with heterozygous FH (mean age 45.2 +/- 15.0 years).
Interventions	Lipid lowering diet & 6 g fish oil ethylester/day for 4 weeks versus lipid lowering diet & 6 g olive oil/day for 4 weeks. 4 week washout period. All patients maintained on lipid lowering medication (simvastatin, dose range 10 - 40 mg) throughout both arms of the trial.
Outcomes	Total cholesterol, HDL, LDL, triglycerides, apolipoprotein A1 &B and Lp(a) concentrations.
Notes	NB. short-term outcomes only will be assessed. 2 patients were withdrawn from the trial and not included in the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants withdrew from one trial due to medical reasons (1 suffered a heart attack and one required vascular surgery) and not included in the final analysis.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Chisholm 1992

Methods	Randomised controlled cross-over trial.
Participants	19 participants (11 females, 8 males) with FH, mean age 51 +/- 10yrs.
Interventions	3 x 8 weeks periods (high fat, low fat, high fat verses low fat, high fat, low fat). Maintained on lipid lowering medication (simvastatin) throughout all arms of trial. Low fat diet = 27% energy from total fat, 8% energy from saturated fat, high fat diet = 38% energy from total fat, 14% energy from saturated fat.
Outcomes	Total & HDL cholesterol, triglycerides and apolipoprotein A1 & B.
Notes	NB. short-term outcomes only will be assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.

Chisholm 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if an intention-to-treat analysis was carried out
Selective reporting (reporting bias)	Low risk	Selective reporting of outcomes was not found

Engler 2004

Methods	Randomised controlled cross-over trial.
Participants	20 participants (9 - 19 years) with FH or familial combined hyperlipidemia.
Interventions	DHA (1.2 gm/day) was combined with NCEP-II diet (6 weeks) followed by placebo after a washout period of 2 weeks.
Outcomes	Total, LDL, VLDL, HDL and triglyceride levels were measured.
Notes	Short-term outcomes only will be assessed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate. No dropouts.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Guardamagna 2011a

Methods	Double-blind, randomised, placebo-controlled, cross-over trial.
Participants	Children with familial hypercholesterolemia (n = 24) and combined familial hyperlipidemia (n = 16).
Interventions	Dietary supplement containing 200 mg red yeast rice extract, corresponding to 3 mg of monacolins, and 10 mg policosanols once-daily (for 8 weeks) versus placebo (for 8 weeks). 4-week washout period.

Guardamagna 2011a *(Continued)*

Outcomes	Total cholesterol, LDL-C, apolipoprotein B, HDL-C.
Notes	No subgroup analysis presented by type of hypercholesterolemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Arbitrary allocation was done but randomisation procedure unclear.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Gylling 1995

Methods	Randomised controlled cross-over trial.
Participants	14 children (7 females, 7 males) with heterozygous FH, mean age 9.1 +/- 1.1 years.
Interventions	Rapeseed oil margarine with or without sitostanol ester for 6 weeks in addition to low fat, low cholesterol diet.
Outcomes	Total, VLDL, HDL & LDL cholesterol, phospholipids & triglycerides & apolipoprotein E.
Notes	NB. Short-term outcomes only will be assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate.

Gylling 1995 *(Continued)*

Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Ketomäki 2003

Methods	Randomised, controlled, cross-over trial.
Participants	Pediatric patients with hypercholesterolaemia with a subgroup of 16 patients who had FH.
Interventions	Low fat diet with plant stanol spread compared with low fat diet with sterol ester spread for 5 weeks; separated by a 5-week washout period.
Outcomes	Total, VLDL, HDL & LDL cholesterol, triglycerides, Apo-B and non-cholesterol sterols.
Notes	NB: Only short term outcomes were assessed, data for the 17 patients with FH not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate. No dropouts.
Selective reporting (reporting bias)	Low risk	No reporting bias was noted

Ketomäki 2004a

Methods	Randomised, cross-over trial.
Participants	5 adult participants with FH.
Interventions	Sterol and stanol for 4 weeks for each treatment period. No washout period described.
Outcomes	Total, HDL & LDL cholesterol, triglycerides.
Notes	Only short-term outcomes were assessed in small number of participants.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Ketomäki 2004a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as a randomised trial.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Included all participants.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Ketomäki 2005

Methods	Randomised, controlled, cross-over trial.
Participants	18 adults (6 males, 12 females) with FH on cholesterol-lowering drug therapy. Mean (SEM) age of 48 (2) years).
Interventions	Low fat plant sterol ester spread or low fat plant stanol ester spread over over and above ongoing drug therapy.
Outcomes	Total, VLDL, HDL & LDL cholesterol, triglycerides, Apo-B and non-cholesterol sterols.
Notes	NB: Only short term outcomes were assessed; No treatment period involved a phase of lipid-lowering drug given alone.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Laurin 1991

Methods	Randomised controlled cross-over trial.
Participants	10 children (4 females, 6 males) with heterozygous FH, aged 6 - 12 years (mean (SD) 8 (1) year).
Interventions	Cows milk diet + regular diet (4 weeks) followed by soy-beverage diet + regular diet (4 weeks) or vice versa. 4 week washout period on regular diet between treatment arms.
Outcomes	Total, HDL, VLDL, LDL cholesterol, triglycerides, phospholipids & apolipoprotein A-1 & B.
Notes	NB. 2 children were excluded from the final analysis. Short term outcomes only will be assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants were withdrawn from the trial for lack of compliance and elevated serum lipid levels and not included in the final analysis.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Neil 2001

Methods	Randomised controlled cross-over trial.
Participants	30 adults with heterozygous FH and 32 with type IIa primary hypercholesterolaemia (26 females), (mean age 51.6 years).
Interventions	A plant sterol-enriched fat spread (8 weeks) versus a control fat spread not enriched with plant sterols (8 weeks). No washout period.
Outcomes	Serum total, HDL, LDL cholesterol, apolipoprotein A-1 and B, liver function tests and plant sterol and cholesterol precursor sterol levels.
Notes	Due to evidence of significant carry-over effect , analysis was restricted to first treatment period only. The authors provided data for only 15 patients with FH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used to assign the participants to either test or the control group with equal probability.

Neil 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Tamper proof block randomisation was used and clinic and lab staff remained unaware of the assigned treatment throughout the trial.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate. No dropouts.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported

Nigon 2001

Methods	Randomised, double-blind,placebo-controlled two-period cross-over trial with 2 treatments and 3 periods.
Participants	53 primary hypercholesterolaemia participants (22 men and 31 women).
Interventions	Spread enriched with plant sterols was compared to non-enriched control spread. 1.6 g/day of plant sterols . The plant sterol content consisted of sitosterol esters (50%), campesterol esters (25%), stigmasterol esters (20%) and 10% of other esters. Treatment periods: 2 months each, with a washout period of 2 months between them.
Outcomes	Total and LDL-C concentrations.
Notes	Fibrates were used additionally in 19 participants.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated randomised, method not described.
Allocation concealment (selection bias)	Unclear risk	A physician allocated each person to one of the treatments for each period such that the design was balanced, in the following order: non-enriched control spread was followed by phytosterol enriched spread or the reverse order.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient did not consume the full amount of intervention and another stopped it for 10 days. Both were included in the analysis.
Selective reporting (reporting bias)	Low risk	No reporting bias was observed.

O'Neill 2004

Methods	Radnomised double blind, parallel trial.
Participants	145 participants recruited, 11 excluded, 134 completed trial. 69 participants with FH (57% female, mean age 53 years), 65 unaffected (69% female, mean age 46 years).
Interventions	3 treatment groups: STE: 1.6g + 1 placebo cereal bar daily; LSTA: 1.6g + 1 placebo cereal bar daily; HS-TA: 1.6 g+ 1 g stanol ester daily. Each treatment lasted 2 months following a 1 month run-in on placebo margarine and followed by a 1-month washout on placebo margarine.
Outcomes	Changes in serum lipids, total and LDL cholesterol, serum apoB and LDL cholesterol: apo B ratios, changes in non-cholesterol sterols (lathosterol, sitosterol, campesterol), changes in 7 alpha OH-cholestenone.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomised" but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the analysis.
Selective reporting (reporting bias)	Low risk	Reporting bias was not present.

Wirth 1982

Methods	Randomized, cross-over trial.
Participants	12 adult patients with familial hypercholesterolemia, 11 out of 12 had an isolated hypercholesterolemia (type IIa).
Interventions	Bezafibrate at a dose of 200 mg t.i.d was prescribed for 2 months during the initial period. First group was given 5.2 g guar t.i.d in a granulate form in addition to the 200 mg bezafibrate t.i.d during the second 2-month period. They were then subsequently treated in the next period of 2 month with bezafibrate alone. In the other group the sequence was reversed.
Outcomes	Serum lipids and lipoprotein levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Wirth 1982 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details not given.
Allocation concealment (selection bias)	Unclear risk	Details not given.
Blinding (performance bias and detection bias) All outcomes	High risk	Details not given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported.

Wolfe 1992

Methods	Randomised controlled cross-over trial.
Participants	5 patients with FH (3 females, 2 males) mean (SD) age 48 (6) years.
Interventions	4 - 5 weeks of high-protein, low-fat diet versus 4 - 5 weeks of low-protein, low-fat diet.
Outcomes	Fasting blood lipoprotein levels (LDL, HDL, VLDL, triglycerides).
Notes	NB. Short term outcomes only will be assessed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was considered adequate.There were no dropouts.
Selective reporting (reporting bias)	Low risk	All the outcomes stated in methods were reported.

FH: familial hypercholesterolaemia
HDL: high density lipoprotein
HSTA: high-dose stanol group
LDL: low density lipoprotein
LSTA: low-dose stanol group

SEM: standard error of the mean
STE: plant sterol ester
VLDL: very low density lipoprotein

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

Study	Reason for exclusion
Abbey 1990	Not FH
Abbey 1993a	Not FH
Abbey 1993b	Not FH
Abrahamson 1974	Not FH, not an RCT
Ahmed 1984	Not FH, not an RCT
Ahrens 1954	Not FH, not an RCT
Ahrens 1957	Not an RCT
Ahrens 1959	Not an RCT
Am Acad Paed 1972	Not an RCT
Amundsen 2004	Non-randomized
Anderson 1957	Not FH, not an RCT
Anderson 1976	Not FH
Anderson 1980	Not FH, not an RCT
Anderson 1984a	Not defined FH
Anderson 1984b	Not defined FH
Asherio 1995	Not FH, not an RCT
Atkinson 1987	Not FH, not an RCT
Baggio 1988	Not an RCT
Bartram 1992	Not an RCT
Becker 1983	Not FH, not an RCT
Becker 1993	Not an RCT
Beil 1991	Not FH
Beitz 1981	Not FH, not an RCT
Berg 1991	Not an RCT
Berge 1959	Not an RCT

Study	Reason for exclusion
Berry 1991	Not FH
Best 1954	Not defined FH
Best 1955	Not defined FH
Best 1956	Not an RCT
Beveridge 1955	Not FH, not an RCT
Beveridge 1957	Not FH, not an RCT
Beveridge 1959	Not FH, not an RCT
Beynen 1985	Not FH, not an RCT
Bierenbaum 1963	Not FH
Bierenbaum 1970	Not defined FH
Blair 2000	No patients with familial hypercholesterolemia
Blankenhorn 1990	Not diet vs diet
Blaton 1984	Not an RCT
Boberg 1986	Not FH
Bonanome 1988	Not defined FH
Bonanome 1992	Not FH
Bowry 1993	Not an RCT
Boyd 1990	Not FH
Braden 1990	Animal study
Brensike 1982	Not defined FH
Brensike 1984	Not defined FH
Brinton 1990	Not in patients with FH
Briones 1984	Drug study
Brongeest 1979a	Not FH
Brongeest 1979b	Not FH
Brongeest 1979c	Not FH, not an RCT
Bronte-Stewart 1956	Not FH, not an RCT
Brown 1991	Not FH, not an RCT

Study	Reason for exclusion
Brox 1981	Not FH
Brox 1983	Not randomized
Bruckner 1987	Not defined FH
Brude 1997	Not defined FH
Brussaard 1980	Not FH, not an RCT
Burr 1989	Not FH
Canetti 1995	Not FH, not diet
Carlson 1971	Not RCT
Carmen-Ramon 1998	Not RCT
Carranza 1997	Not defined FH
Carroll 1975	Not RCT
Carroll 1978	Animal studies
Carroll 1982	Review article
Carroll 1991	Not RCT
Chait 1974	Not FH
Chang 1990	Not FH, not RCT
Chen 1979	Animal studies
Chenoweth 1981	Not FH, not RCT
Childs 1981	Not an RCT
Clevidence 1992	Not FH, not RCT
Clifton 1992	Not defined FH
Cobb 1991	Not defined FH
Cole 1992	Not an RCT
Colquhoun 1992	Not FH, not RCT
Connor 1961a	Not FH, not RCT
Connor 1961b	Not FH, not RCT
Connor 1964	Not FH, not RCT
Connor 1982	Not FH, not RCT

Study	Reason for exclusion
Corder 1989	Drug study
Cortese 1983	Not defined FH
Crouse 1979	Not FH, not RCT
Da Col 1984	Drug study
Dattilo 1992	Not an RCT
Davidson 1991	Not FH
Davis 1985	Drug study
de Groot 1963	Animal study
De Jong 2008	No F H pts
Demke 1988	Not defined FH
Demke 1991	Not defined FH
Denke 1995	Not defined FH
Descovich 1980	Not an RCT
Detre 1985	Not defined FH
Dieber 1991	Not FH, not RCT
Dreon 1990	Not FH, not RCT
Dreon 1994	Not FH
Dreon 1997	Not RCT
Durrington 1977	Not FH, not RCT
Dyerberg 1978	Not RCT
East 1988	Drug study
Edington 1989	Not RCT
Ehnholm 1982	Not RCT
Ehnholm 1984	Not in patients with FH
Elkeles 1988	Not RCT
Erickson 1964	Not FH, not RCT
Eritsland 1995	Not FH
Ernst 1980	Not RCT

Study	Reason for exclusion
Failor 1986	Not FH
Falko 1980	Not FH, not RCT
Fallat 1979	Not RCT
Farquhar 1956	Not RCT
Farquhar 1958	Not defined FH
Fehily 1983	Not FH
Fernandes 1977	Not RCT, drug study
Fernandes 1981	Not RCT
Ferro-Luzzi 1984	Not FH, not RCT
Fisher 1983	Not FH, not RCT
Flaim 1981	Not FH
Flynn 1981	Not FH, not RCT
Follick 1984	Not FH, not RCT
Forsythe 1986	Review article, not RCT
Frank 1978	Not RCT
Frankel 1994	Not FH
Frantz 1975	Not FH
Frantz 1989	Not FH
Friday 1991	Not cholesterol-lowering diet
Fumagalli 1978	Animal study
Fumagalli 1982	Not RCT, not defined FH
Gaddi 1987	Not RCT
Galvan 1996	Drug study
Gardner 1995	Not RCT
Gardner 2005	Not in patients with FH
Glueck 1972	Not RCT
Glueck 1977	Not RCT
Glueck 1978	Not RCT

Study	Reason for exclusion
Glueck 1979	Not RCT
Glueck 1983	Not RCT
Glueck 1991	Not RCT
Goldberg 1982	Not defined FH
Goodnight 1981	Not FH
Gordon 1977	Not FH, not RCT
Gordon 1982	Non-interventional study
Grande 1970	Not FH
Grande 1972	Not FH
Gries 1990	Not FH, not RCT
Groot 1980	Drug study
Grundy 1970	Not RCT
Grundy 1986	Not defined FH
Grundy 1990	Not RCT
Guardamagna 2011b	Natural HMGCoA inhibitor used
Gustafsson 1982	Not RCT
Gustafsson 1983	Not defined FH
Gustafsson 1985	Not defined FH
Gustafsson 1992	Not defined FH
Gustafsson 1994	Not defined FH
Gylling 1988	Not RCT
Gylling 2010	Not in patients with FH
Gylling 2011	Not in patients with FH
Hansen 1989	Study in healthy volunteers
Harris 1983a	Not FH
Harris 1988	Not FH
Harris 1989	Not RCT
Hashim 1960	Not RCT

Study	Reason for exclusion
Hay 1982	Not RCT
Hegsted 1965	Not FH, not RCT
Hegsted 1986	Not RCT
Hegsted 1993	Not RCT
Heinemann 1986	Not RCT
Helms 1977	Not RCT
Hennekens 1996	Not FH
Herold 1986	Not RCT
Hodges 1967	Not FH, not RCT
Hoeg 1984	Drug study
Holme 1990	Not RCT
Holmes 1980	Not in patients with FH.
Hooper 1980	Not FH, not RCT
Hopkins 1992	Not RCT
Huff 1984	Not defined FH
Hunninghake 1993	Not defined FH
Iacono 1991	Not FH
Illingworth 1991	Not defined FH
Jackson 1984	Not FH, not RCT
Jakubowski 1978	Not FH, not RCT
Jenkins 1975a	Not FH, not RCT
Jenkins 1975b	Not FH, not RCT
Jenkins 1980	Not RCT
Jialal 1992	Not FH
Jialal 1993	Not FH
Joyner 1955	Not defined FH
Judd 1988	Participants did not have familial hypercholesterolemia
Kane 1981	Drug study

Study	Reason for exclusion
Kane 1990	Drug study
Kestin 1989	Not FH
Ketomäki 2004b	Not RCT
Keys 1957	Not RCT
Keys 1965a	Not RCT
Keys 1965b	Not RCT
Keys 1984	Not RCT
Khan 1981	Not FH
Kingsbury 1961	Not FH, not RCT
Kinsell 1952	Not RCT
Kirby 1981	Not defined FH
Kok 1987	Not RCT
Kris-Etherton 1993	Not FH
Kromhout 1985	Not RCT
Kudchodkar 1976	Not RCT
Kuo 1979	Drug study
Kuo 1981	Not RCT
Kuusi 1985	Not FH
Laine 1982	Not FH, not RCT
Lambert 1996	Drug study
Leaf 1988	Not RCT
Leelarthaepin 1974	Not RCT
Lees 1977	Not RCT
Leibman 1983	Not FH, not RCT
LeLorier 1977	Drug study
Lewis 1981	Not FH
Lichtenstein 1994	Not RCT
Lifshitz 1989	Not RCT

Study	Reason for exclusion
Lindgard 1984	Not defined FH
Linnebur 2007	No FH pts
Lithell 1984	Not defined FH
Lorenz 1983	Not FH, not RCT
Lovati 1987	Not defined FH
LRCP 1984a	Drug study
LRCP 1984b	Drug study
Macdonald 1967	Not FH, not RCT
Mackness 1993	Not RCT Not FH
Malmros 1957	Not RCT
Mannarinno 2009	No F H pts
Maranhao 1983	Not RCT
Marshall 1986	Not FH
Mata 1992	Not FH, not RCT
Mathur 1968	Not FH, not RCT
Mattson 1972	Not FH
Mattson 1975	Not FH, not RCT
Mattson 1977	Animal study
Mattson 1982	Not RCT
Mattson 1985	Not defined FH
McCombs 1994	Not RCT
McGill 1979	Not RCT
Mellies 1983	Not defined FH
Mensink 1992	Not RCT
Miettinen 1972	Not FH, not RCT
Miettinen 1977	Not RCT
Miettinen 1989a	Not FH, not RCT

Study	Reason for exclusion
Miettinen 1989b	Not FH, not RCT
Miettinen 1992a	Study not relevant
Miettinen 1992b	Not FH
Miettinen 1994	Not defined FH
Miller 1988	Not FH
Mokino 1990	Not RCT
Morita 1983	Animal study
MRC 1965	Not FH
MRC 1968	Not FH
Nagakawa 1983	Not FH, not RCT
Napoli 1998	Not defined FH
NDHSRG 1968	Not FH
Neil 1995	Not FH
Nenseter 1992	Not FH
Nessim 1983	Not defined FH, drug study
Nestel 1973	Not RCT
Nestel 1976	Not FH, not RCT
Nestel 1984	Not FH, not RCT
Nestel 1986	Not FH, not RCT
Nestel 1992a	Not defined FH
Nestel 1992b	Not FH
Nilson 1991	Not FH
Nydahl 1994	Not defined FH
Nyyssonen 1994	Not FH
Olszewski 1993	Not defined FH
Omenn 1996	Not FH
Ordovas 1995	Not RCT
Parks 1990	Animal study

Study	Reason for exclusion
Parthasarathy 1990	Animal study
Peto 1985	Not RCT
Phillipson 1985	Not defined FH
Pirich 1999	Not defined FH
Princen 1995	Not RCT, not FH
Quintao 1971	Not RCT
Radack 1989	Not defined FH
Radack 1990	Not defined FH
Rapola 1996	Not defined FH
Reaven 1991	Not FH
Reaven 1993a	Not FH
Reaven 1993b	Not defined FH
Reaven 1993c	Not FH, not RCT
Reaven 1994	Not FH
Reiser 1985	Not FH
Retzloff 1991	Not defined FH
Riccardi 1987	Review article
Rivellese 1994	Not defined FH
Roberts 1994	Not RCT
Rona 1985	Not FH, not RCT
Rose 1976	Not RCT
Rosenthal 1985	Not RCT
Sacks 1986	Not FH
Sanders 1981	Not FH
Sanders 1983	Not FH
Sanders 1984	Not in patients with FH
Saynor 1982a	Not RCT
Saynor 1984a	Not RCT

Study	Reason for exclusion
Saynor 1984b	Not FH
Schaefer 1981	Not RCT
Schectman 1989	Not FH, not RCT
Schlierf 1982	Drug study
Schonfeld 1982	Not FH, not RCT
Schwandt 1982	Not FH, not RCT
Segall 1970	Not RCT
Seppanen-Laakso 1992	Not FH
Seppanen-Laakso 1993	Not FH, not RCT
Shepherd 1978	Not FH
Shepherd 1980	Not FH, not RCT
Shorey 1981	Not FH, not RCT
Siess 1980	Not FH, not RCT
Simons 1985a	Not defined FH
Simons 1985b	Not defined FH
Singer 1983	Not FH, not RCT
Singer 1984	Not defined FH
Singer 1986	Not defined FH
Sirtori 1977	Not FH, not RCT
Sirtori 1979	Not defined FH
Sirtori 1981	Not RCT
Sirtori 1986	Not defined FH
Sirtori 1992	Not FH
Sperling 1987	Not FH, not RCT
Stein 1975	Not FH, not RCT
Stein 1982	Not RCT
Stephens 1996	Not defined FH
Subbaiah 1989	Not RCT

Study	Reason for exclusion
Sucic 1998	Not defined FH
Szczeklik 1985	Not defined FH
Thorngren 1981	Not FH, not RCT
Thorngren 1984	Not FH, not RCT
Thorngren 1986	Not FH, not RCT
Tonstad 1997b	Not RCT
Ullmann 1990	Drug study
Uusitupa 1991	Comparison not per protocol
Valsta 1992	Not FH, not RCT
Van Gent 1979	Not FH, not RCT
Van Horn 1986	Not FH
Vanhanen 1991	Not RCT
Vanhanen 1993	Not defined FH
Vanhanen 1994	Not defined FH
Varady 2007	No FH pts
Vega 1982	Not RCT
Verrillo 1985	Not defined FH
Vessby 1980a	Not RCT
Vessby 1980b	Not RCT
Vessby 1982	Not RCT
Von Schacky 1985	Not FH, not RCT
Von Schacky 1987	Not RCT
Vuorio 2000	Non-randomized
Wardlaw 1990	Not FH
Weisweiler 1983	Not FH, not RCT
Weisweiler 1985	Not FH, not RCT
Widhalm 1978	Not defined FH
Widhalm 1993	Not defined FH

Study	Reason for exclusion
Williams 1986	Not FH, not RCT
Wilson 1971	Not RCT
Wilt 1989	Not defined FH
Witters 1976	Not RCT
Wolf 1983	Not RCT
Wolfe 1991	Not FH
Worne 1959	Not defined FH
Yacowitz 1965	Not FH, not RCT
Zhao 1993	Not defined FH, drug study
Zimmerman 1986	Not FH, not RCT
Zino 1987	Not FH
Zock 1992	Not FH
Zucker 1983	Not defined FH, drug study
Zucker 1988	Not defined FH

RCT=Randomised controlled trial
FH=Familial hypercholesterolaemia

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

Fuentes 2008

Methods	Randomised and cross-over dietary intervention trial.
Participants	38 participants with FH were recruited, but only 30 were subjected to 4 low-fat dietary intervention periods.
Interventions	4 low-fat dietary intervention periods, each of 4 weeks. Each intervention had a different content of cholesterol (< 150 or 300 mg/day) and sitosterol (< 1 or 2 g/day).
Outcomes	Plasma sitosterol/cholesterol ratio, basal sitosterol concentrations, change in LDL-C.
Notes	Duration of intervention 4 weeks.

Stein 2007

Methods	Open-label, non-comparative, multicenter study.

Stein 2007 *(Continued)*

Participants	1380 individuals with severe hypercholesterolaemia, including heterozygous familial hypercholesterolaemia. Individuals were 18 years old or over with fasting LDL-C greater than or equal to 190 and less than or equal to 260 mg/dl and triglycerides under 400 mg/dl.
Interventions	Rosuvastatin 40 mg for 48 weeks. An optional additional 48-week treatment period followed.
Outcomes	The initial period had 2 primary end points: percentage of patients achieving National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III LDL cholesterol goals at 12 weeks, and long-term safety, assessed during 48 weeks by incidence and severity of adverse events and abnormal laboratory values. Safety was the primary end point in the extension period.
Notes	6-week dietary lead-in.

FH: familial hypercholesterolaemia
LDL-C: low density lipoprotein cholesterol

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

Párraga ongoing

Trial name or title	Párraga 2011.
Methods	Randomised, double-blind, placebo controlled trial.
Participants	Adults with "limit" or "defined" hypercholesterolaemia and who have LDL cholesterol levels of 130 mg/dl or over.
Interventions	Yoghurt containing 2 g of plant sterol ester per container versus yoghurt without sterol for 24 months.
Outcomes	Change in lipid profile at 1, 3, 6, 12, 18 and 24 months.
Starting date	
Contact information	iparraga@sescam.jccm.es
Notes	

DATA AND ANALYSES

Comparison 1. Cholesterol-lowering diet compared to no dietary intervention or nutritional advice

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting serum total cholesterol concentration (mmol/l)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Over one month and up to two months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Fasting serum LDL cholesterol concentration (mmol/l)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Over one month and up to two months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Fasting serum HDL cholesterol concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Over one month and up to two months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Fasting serum triglyceride concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Over one month and up to two months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Fasting serum apolipoprotein A1 concentration (g/l)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Over one month and up to two months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Fasting serum apolipoprotein B-100 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Over one month and up to two months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 1 Fasting serum total cholesterol concentration (mmol/l).

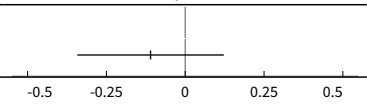
Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.1.1 Over one month and up to two months						
Chisholm 1992	19	6 (0.8)	19	6.4 (1)		-0.4[-0.95,0.15]

Analysis 1.2. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.2.1 Over one month and up to two months						
Chisholm 1992	19	4 (0.7)	19	4.2 (0.9)		-0.27[-0.79,0.25]

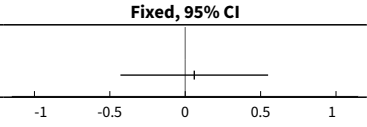
Analysis 1.3. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 Over one month and up to two months						
Chisholm 1992	19	1.3 (0.4)	19	1.4 (0.4)		-0.11[-0.34,0.12]



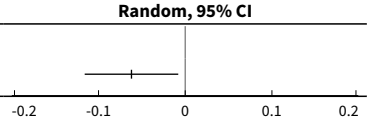
Analysis 1.4. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 4 Fasting serum triglyceride concentration (mmol/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.4.1 Over one month and up to two months						
Chisholm 1992	19	1.6 (0.8)	19	1.5 (0.8)		0.06[-0.43,0.55]



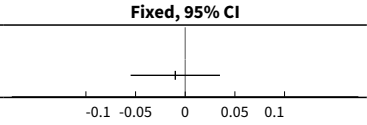
Analysis 1.5. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 5 Fasting serum apolipoprotein A1 concentration (g/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.5.1 Over one month and up to two months						
Chisholm 1992	19	1.4 (0)	19	1.5 (0.1)		-0.06[-0.12,-0.01]



Analysis 1.6. Comparison 1 Cholesterol-lowering diet compared to no dietary intervention or nutritional advice, Outcome 6 Fasting serum apolipoprotein B-100 concentration (g/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	No diet intervention N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.6.1 Over one month and up to two months						
Chisholm 1992	19	1 (0)	19	1 (0.1)		-0.01[-0.05,0.03]



Comparison 2. ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet

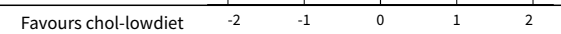
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting serum total cholesterol concentration (mmol/l)	2	68	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.80, 0.69]
1.1 Up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.84, 0.94]
1.2 Over one month and up to two months	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.62, 1.04]
2 Fasting serum LDL cholesterol concentration (mmol/l)	2	68	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.93, 0.69]
2.1 Up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.99, 0.95]
2.2 Over one month and up to two months	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-1.79, 1.11]
3 Fasting serum HDL cholesterol concentration (mmol/l)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.10, 0.13]
3.1 Up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.40, 0.34]
3.2 Over one month and up to two months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.10, 0.14]
4 Fasting serum triglyceride concentration (mmol/l)	2	68	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.07, 0.43]
4.1 Up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.14, 0.62]
4.2 Over one month and up to two months	1	40	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.21, 0.47]
5 Fasting serum apolipoprotein A1 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Fasting serum apolipoprotein B-100 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 1 Fasting serum total cholesterol concentration (mmol/l).

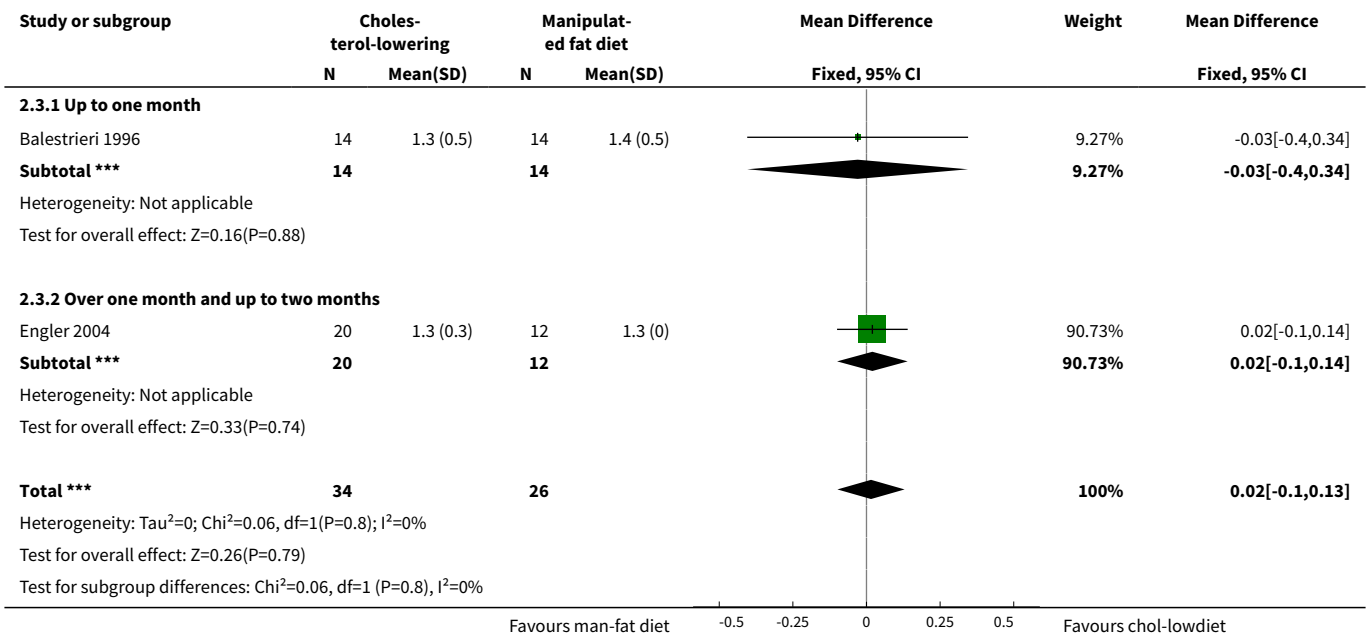
Study or subgroup	Choles-terol-lowering N	Mean(SD)	Manipulat-ed fat diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Up to one month							
Balestrieri 1996	14	7.8 (1.1)	14	7.8 (1.3)		68.88%	0.05[-0.84,0.94]
Subtotal ***	**14**		**14**			**68.88%**	**0.05[-0.84,0.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.11(P=0.91)							
2.1.2 Over one month and up to two months							
Engler 2004	20	7.4 (2.2)	20	7.7 (2.1)		31.12%	-0.29[-1.62,1.04]
Subtotal ***	**20**		**20**			**31.12%**	**-0.29[-1.62,1.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.67)							
Total ***	**34**		**34**			**100%**	**-0.06[-0.8,0.69]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%							
Test for overall effect: Z=0.15(P=0.88)							
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.68), I^2=0%							

Analysis 2.2. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

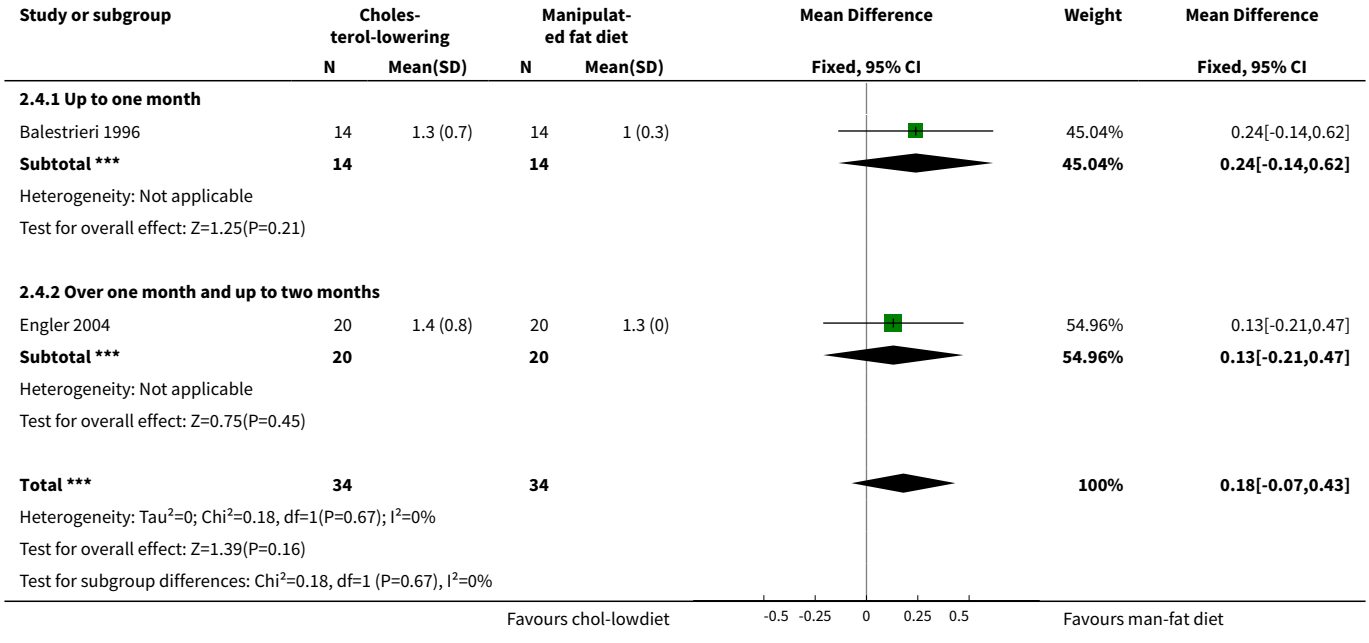
Study or subgroup	Choles-terol-lowering N	Mean(SD)	Manipulat-ed fat diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 Up to one month							
Balestrieri 1996	14	5.9 (1.3)	14	5.9 (1.3)		69.02%	-0.02[-0.99,0.95]
Subtotal ***	**14**		**14**			**69.02%**	**-0.02[-0.99,0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.04(P=0.97)							
2.2.2 Over one month and up to two months							
Engler 2004	20	5.5 (2.5)	20	5.9 (2.2)		30.98%	-0.34[-1.79,1.11]
Subtotal ***	**20**		**20**			**30.98%**	**-0.34[-1.79,1.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.46(P=0.65)							
Total ***	**34**		**34**			**100%**	**-0.12[-0.93,0.69]**
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%							
Test for overall effect: Z=0.29(P=0.77)							
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.72), I^2=0%							



Analysis 2.3. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).



Analysis 2.4. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 4 Fasting serum triglyceride concentration (mmol/l).



Analysis 2.5. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 5 Fasting serum apolipoprotein A1 concentration (g/l).

Study or subgroup	Cholesterol-lowering N	Cholesterol-lowering Mean(SD)	Manipulated fat diet N	Manipulated fat diet Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.5.1 Up to one month						
Balestrieri 1996	14	1.3 (0.4)	14	1.3 (0.5)		-0.02[-0.35,0.31]

Analysis 2.6. Comparison 2 ω-fatty acids added to background cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 6 Fasting serum apolipoprotein B-100 concentration (g/l).

Study or subgroup	Cholesterol-lowering N	Cholesterol-lowering Mean(SD)	Manipulated fat diet N	Manipulated fat diet Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.6.1 Up to one month						
Balestrieri 1996	14	2.1 (0.4)	14	2 (42)		0.01[-21.99,22.01]

Comparison 3. Plant stanols added to cholesterol-lowering diet compared to cholesterol-lowering diet alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting serum total cholesterol concentration (mmol/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Over one month and up to two months	2	38	Mean Difference (IV, Fixed, 95% CI)	0.51 [0.07, 0.96]
2 Fasting serum LDL cholesterol concentration (mmol/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Over one month and up to two months	2	38	Mean Difference (IV, Fixed, 95% CI)	0.71 [0.43, 0.99]
3 Fasting serum HDL cholesterol concentration (mmol/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Over one month and up to two months	2	38	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.15, -0.00]
4 Fasting serum triglyceride concentration (mmol/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Over one month and up to two months	2	38	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.22, 0.27]

Analysis 3.1. Comparison 3 Plant stanols added to cholesterol-lowering diet compared to cholesterol-lowering diet alone, Outcome 1 Fasting serum total cholesterol concentration (mmol/l).

Study or subgroup	Choles-terol-lowering N	Mean(SD)	Plant stanols N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 Over one month and up to two months							
Gylling 1995	14	7.6 (1.2)	14	6.8 (1.3)		23.46%	0.81[-0.11,1.73]
Ketomäki 2004a	5	6 (0.5)	5	5.5 (0.3)		76.54%	0.42[-0.08,0.93]
Subtotal ***	**19**		**19**			**100%**	**0.51[0.07,0.96]**
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%							
Test for overall effect: Z=2.28(P=0.02)							

Favours chol-lowdiet — Favours stanol diet

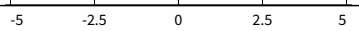
Analysis 3.2. Comparison 3 Plant stanols added to cholesterol-lowering diet compared to cholesterol-lowering diet alone, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

Study or subgroup	Choles-terol-lowering N	Mean(SD)	Plant stanols N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.2.1 Over one month and up to two months							
Gylling 1995	14	5.5 (1.1)	14	4.7 (1.2)		10.47%	0.82[-0.04,1.68]
Ketomäki 2004a	5	4.8 (0.3)	5	4.1 (0.1)		89.53%	0.7[0.41,0.99]
Subtotal ***	**19**		**19**			**100%**	**0.71[0.43,0.99]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=5.02(P<0.0001)							

Favours chol-lowdiet — Favours plant stanol

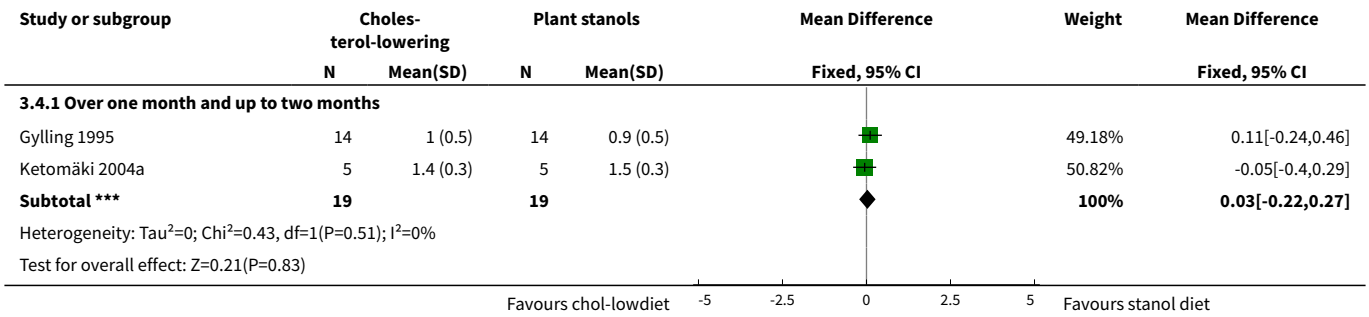
Analysis 3.3. Comparison 3 Plant stanols added to cholesterol-lowering diet compared to cholesterol-lowering diet alone, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).

Study or subgroup	Choles-terol-lowering N	Mean(SD)	Plant stanols N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.3.1 Over one month and up to two months							
Gylling 1995	14	1.2 (0.3)	14	1.3 (0.3)		13.12%	-0.05[-0.26,0.16]
Ketomäki 2004a	5	1.3 (0.1)	5	1.4 (0.1)		86.88%	-0.08[-0.16,0]
Subtotal ***	**19**		**19**			**100%**	**-0.08[-0.15,-0]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%							
Test for overall effect: Z=1.98(P=0.05)							



Favours plant stanol — Favours chol-lowdiet

Analysis 3.4. Comparison 3 Plant stanols added to cholesterol-lowering diet compared to cholesterol-lowering diet alone, Outcome 4 Fasting serum triglyceride concentration (mmol/l).

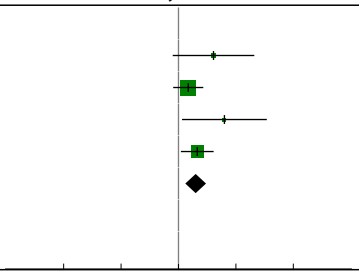


Comparison 4. Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Fasting serum total cholesterol con-centration(mmol/l)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Over one month and up to two months	4	222	Mean Difference (IV, Fixed, 95% CI)	0.30 [0.12, 0.48]
2 Fasting serum LDL cholesterol con-centration (mmol/l)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Over one month and up to two months	4	222	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.89, -0.31]
3 Fasting serum HDL cholesterol con-centration (mmol/l)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Over one month and up to two months	4	222	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.11, 0.03]
4 Fasting serum triglyceride concen-tration (mmol/l)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Over one month and up to two months	4	222	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.09]
5 Fasting serum apolipoprotein A1concentration (g/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Over one month and up to two months	2	182	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.08, 0.14]
6 Fasting serum apolipoprotein B-100 concentratiom (g/l)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Over one month and up to two months	2	182	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.09, 0.13]

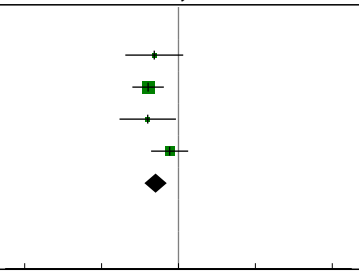
Analysis 4.1. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 1 Fasting serum total cholesterol concentration(mmol/l).

Study or subgroup	Chol lowering diet N	Chol lowering diet Mean(SD)	Plant sterols N	Plant sterols Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.1.1 Over one month and up to two months							
Amundsen 2002	38	7.5 (1.7)	38	6.9 (1.5)		6.46%	0.61[-0.1,1.32]
Ketomäki 2004a	5	2.6 (0.2)	5	2.4 (0.2)		47.42%	0.17[-0.09,0.43]
Neil 2001	15	7 (1.3)	15	6.2 (0.7)		5.98%	0.8[0.06,1.54]
Nigon 2001	53	2.7 (0.6)	53	2.4 (0.9)		40.14%	0.33[0.04,0.61]
Subtotal ***	**111**		**111**			**100%**	**0.3[0.12,0.48]**
Heterogeneity: Tau^2=0; Chi^2=3.47, df=3(P=0.32); I^2=13.6%							
Test for overall effect: Z=3.25(P=0)							



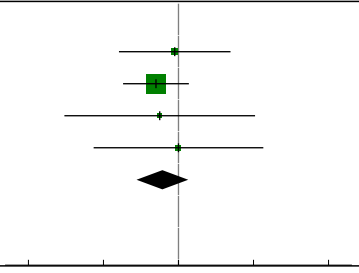
Analysis 4.2. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

Study or subgroup	Plant sterols N	Plant sterols Mean(SD)	Choles-terol-lowering N	Choles-terol-lowering Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.2.1 Over one month and up to two months							
Amundsen 2002	38	5.3 (1.6)	38	5.9 (1.8)		13.89%	-0.63[-1.38,0.12]
Ketomäki 2004a	5	4 (0.3)	5	4.8 (0.3)		40.6%	-0.79[-1.2,-0.38]
Neil 2001	15	3.9 (0.8)	15	4.7 (1.2)		14.58%	-0.8[-1.53,-0.07]
Nigon 2001	53	4.1 (1.4)	53	4.4 (1.1)		30.93%	-0.23[-0.71,0.25]
Subtotal ***	**111**		**111**			**100%**	**-0.6[-0.89,-0.31]**
Heterogeneity: Tau^2=0.01; Chi^2=3.38, df=3(P=0.34); I^2=11.36%							
Test for overall effect: Z=4.02(P<0.0001)							



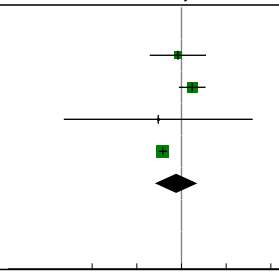
Analysis 4.3. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).

Study or subgroup	Choles-terol-lowering N	Choles-terol-lowering Mean(SD)	Plant sterols N	Plant sterols Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.3.1 Over one month and up to two months							
Amundsen 2002	38	1.3 (0.3)	38	1.3 (0.4)		21.5%	-0.01[-0.16,0.14]
Ketomäki 2004a	5	1.3 (0.1)	5	1.4 (0.1)		61.85%	-0.06[-0.15,0.03]
Neil 2001	15	1.4 (0.4)	15	1.5 (0.4)		7.36%	-0.05[-0.3,0.2]
Nigon 2001	53	1.7 (0.6)	53	1.7 (0.6)		9.29%	0[-0.23,0.23]
Subtotal ***	**111**		**111**			**100%**	**-0.04[-0.11,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.48, df=3(P=0.92); I^2=0%							
Test for overall effect: Z=1.22(P=0.22)							



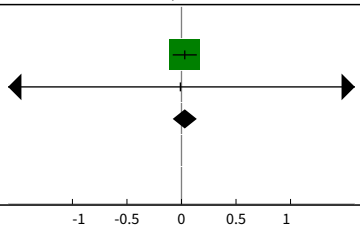
Analysis 4.4. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 4 Fasting serum triglyceride concentration (mmol/l).

Study or subgroup	Plant sterols N	Plant sterols Mean(SD)	Choles-terol-lowering N	Choles-terol-lowering Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.4.1 Over one month and up to two months							
Amundsen 2002	38	0.8 (0.3)	38	0.8 (0.4)		23.15%	-0.02[-0.18,0.14]
Ketomäki 2004a	5	1.4 (0.1)	5	1.3 (0.1)		33.89%	0.06[-0.01,0.13]
Neil 2001	15	1.4 (0.5)	15	1.5 (0.9)		4.48%	-0.13[-0.66,0.4]
Nigon 2001	53	1.1 (0.1)	53	1.2 (0.1)		38.48%	-0.1[-0.13,-0.08]
Subtotal ***	**111**		**111**			**100%**	**-0.03[-0.15,0.09]**
Heterogeneity: Tau²=0.01; Chi²=17.73, df=3(P=0); I²=83.08%							
Test for overall effect: Z=0.5(P=0.62)							



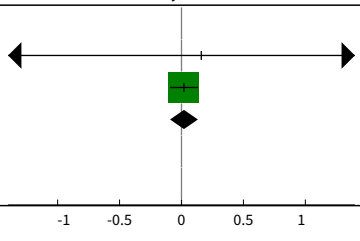
Analysis 4.5. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 5 Fasting serum apolipoprotein A1concentration (g/l).

Study or subgroup	Choles-terol-lowering N	Choles-terol-lowering Mean(SD)	Plant sterols N	Plant sterols Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.5.1 Over one month and up to two months							
Amundsen 2002	38	1.4 (0.2)	38	1.3 (0.3)		99.99%	0.03[-0.08,0.14]
Nigon 2001	53	1.7 (0.4)	53	1.7 (34)		0.01%	-0.01[-9.16,9.14]
Subtotal ***	**91**		**91**			**100%**	**0.03[-0.08,0.14]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%							
Test for overall effect: Z=0.53(P=0.59)							



Analysis 4.6. Comparison 4 Plant sterols added to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 6 Fasting serum apolipoprotein B-100 concentratiom (g/l).

Study or subgroup	Choles-terol-lowering N	Choles-terol-lowering Mean(SD)	Plant sterols N	Plant sterols Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.6.1 Over one month and up to two months							
Amundsen 2002	38	1.5 (0.4)	38	1.3 (35)		0.01%	0.16[-10.97,11.29]
Nigon 2001	53	1.2 (0.3)	53	1.2 (0.3)		99.99%	0.02[-0.09,0.13]
Subtotal ***	**91**		**91**			**100%**	**0.02[-0.09,0.13]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.98); I²=0%							
Test for overall effect: Z=0.35(P=0.73)							



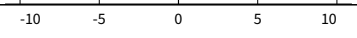
Comparison 5. Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting serum total cholesterol concentration (mmol/l)	2	28	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.65, 0.81]
1.1 Up to one month	1	18	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.94, 0.94]
1.2 Over one month and up to two months	1	10	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.94, 1.34]
2 Fasting serum LDL cholesterol concentration (mmol/l)	2	28	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.46, 0.69]
2.1 Up to one month	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-1.02, 0.94]
2.2 Over one month and up to two months	1	10	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.51, 0.91]
3 Fasting serum HDL cholesterol concentration (mmol/l)	2	28	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.23, 0.08]
3.1 Up to one month	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.23, 0.13]
3.2 Over one month and up to two months	1	10	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.49, 0.17]
4 Fasting serum triglyceride concentration (mmol/l)	2	28	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.01, 0.50]
4.1 Up to one month	1	18	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.05, 0.49]
4.2 Over one month and up to two months	1	10	Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.33, 1.33]
5 Fasting serum apolipoprotein A1 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Fasting serum apolipoprotein B-100 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Height (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Body mass index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Up to one month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 1 Fasting serum total cholesterol concentration (mmol/l).

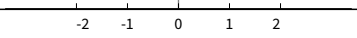
Study or subgroup	Choles-terol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 Up to one month							
Laurin 1991	9	7.9 (1)	9	7.9 (1)		59.57%	0[-0.94,0.94]
Subtotal ***	**9**		**9**			**59.57%**	**0[-0.94,0.94]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.1.2 Over one month and up to two months							
Wolfe 1992	5	7.3 (0.7)	5	7.1 (1.1)		40.43%	0.2[-0.94,1.34]
Subtotal ***	**5**		**5**			**40.43%**	**0.2[-0.94,1.34]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.34(P=0.73)							
Total ***	**14**		**14**			**100%**	**0.08[-0.65,0.81]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%							
Test for overall effect: Z=0.22(P=0.83)							
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%							



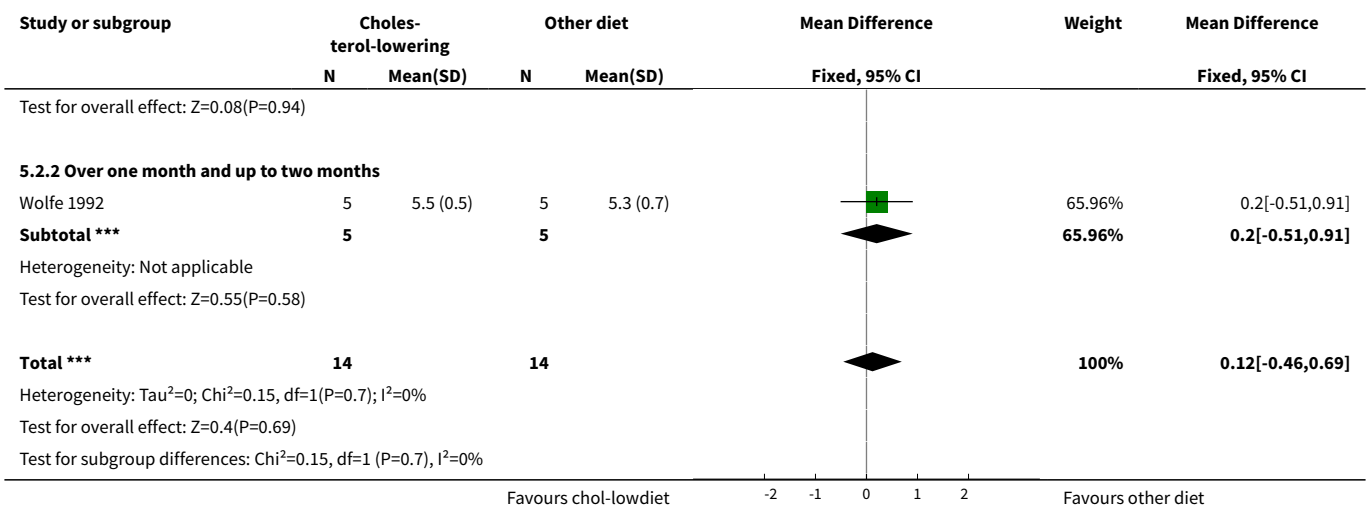
Favours chol-lowdiet — Favours other diet

Analysis 5.2. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

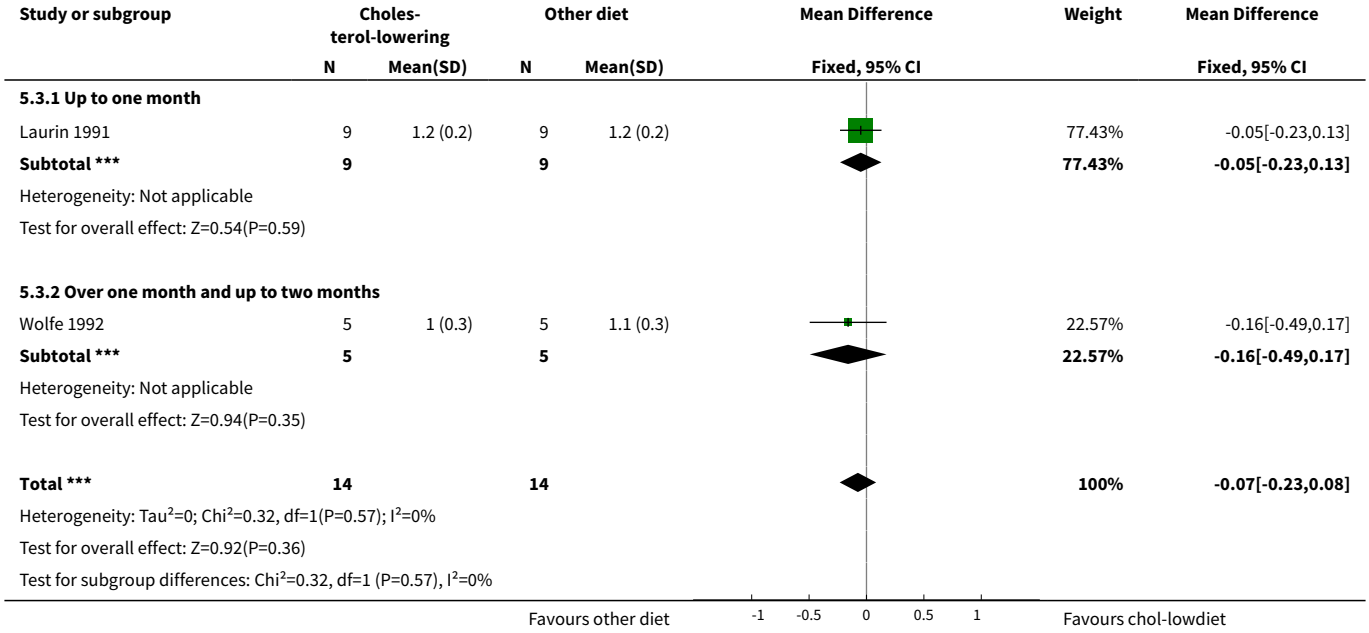
Study or subgroup	Choles-terol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.2.1 Up to one month							
Laurin 1991	9	6.3 (1.1)	9	6.3 (1)		34.04%	-0.04[-1.02,0.94]
Subtotal ***	**9**		**9**			**34.04%**	**-0.04[-1.02,0.94]**
Heterogeneity: Not applicable							



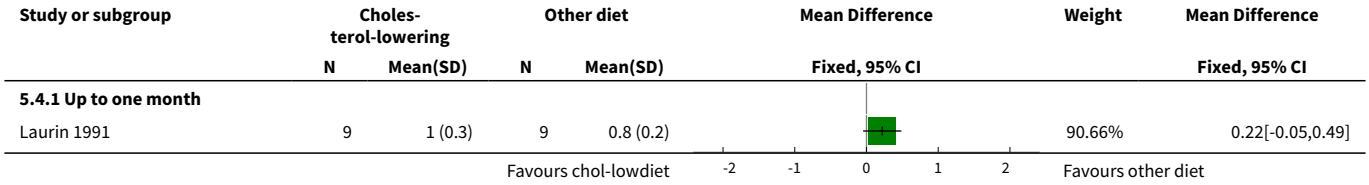
Favours chol-lowdiet — Favours other diet



Analysis 5.3. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).



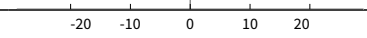
Analysis 5.4. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 4 Fasting serum triglyceride concentration (mmol/l).



Study or subgroup	Choles-terol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**9**		**9**			**90.66%**	**0.22[-0.05,0.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.62(P=0.11)							
5.4.2 Over one month and up to two months							
Wolfe 1992	5	2.2 (0.7)	5	1.7 (0.7)		9.34%	0.5[-0.33,1.33]
Subtotal ***	**5**		**5**			**9.34%**	**0.5[-0.33,1.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							
Total ***	**14**		**14**			**100%**	**0.25[-0.01,0.5]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=1.9(P=0.06)							
Test for subgroup differences: Chi^2=0.4, df=1 (P=0.53), I^2=0%							

Analysis 5.5. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 5 Fasting serum apolipoprotein A1 concentration (g/l).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.5.1 Up to one month						
Laurin 1991	9	1.6 (0.2)	9	1.6 (9)		0.04[-5.84,5.92]



Analysis 5.6. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 6 Fasting serum apolipoprotein B-100 concentration (g/l).

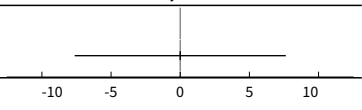
Study or subgroup	Cholesterol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.6.1 Up to one month						
Laurin 1991	9	1.4 (0.2)	9	1.4 (6)		0[-3.92,3.92]

Analysis 5.7. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 7 Weight (kg).

Study or subgroup	Cholesterol-lowering N	Mean(SD)	Other diet N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.7.1 Up to one month						
Laurin 1991	9	28.8 (8.2)	9	28.8 (8.2)		0[-7.58,7.58]

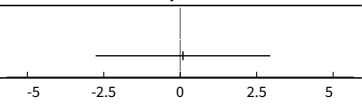
Analysis 5.8. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 8 Height (cm).

Study or subgroup	Cholesterol-lowering N	Cholesterol-lowering Mean(SD)	Other diet N	Other diet Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.8.1 Up to one month						
Laurin 1991	9	130.3 (8)	9	130.3 (8.5)		0[-7.63,7.63]



Analysis 5.9. Comparison 5 Soy protein in addition to cholesterol-lowering diet compared to cholesterol-lowering diet, Outcome 9 Body mass index.

Study or subgroup	Cholesterol-lowering N	Cholesterol-lowering Mean(SD)	Other diet N	Other diet Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.9.1 Up to one month						
Laurin 1991	9	16.8 (3.1)	9	16.7 (3.1)		0.09[-2.77,2.95]

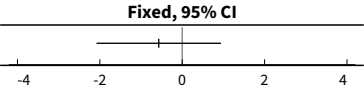


Comparison 6. Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting serum total cholesterol concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Fasting serum LDL cholesterol concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Fasting serum HDL cholesterol concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Fasting serum triglyceride concentration (mmol/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Fasting serum apolipoprotein A1 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Fasting serum apolipoprotein B-100 concentration (g/l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Weight	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 1 Fasting serum total cholesterol concentration (mmol/l).

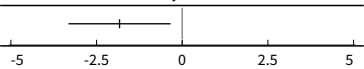
Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	8.5 (1.8)	12	9.1 (2)		-0.57[-2.08,0.94]



Favours bez & guar gum — Favours bezafibrate

Analysis 6.2. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 2 Fasting serum LDL cholesterol concentration (mmol/l).

Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	6.1 (1.9)	12	7.9 (1.8)		-1.83[-3.32,-0.34]



Favours bez with guar gum — Favours bezafibrate

Analysis 6.3. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 3 Fasting serum HDL cholesterol concentration (mmol/l).

Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	1.2 (0.3)	12	1.4 (0.4)		-0.18[-0.46,0.1]

Favours bez with guar gum — Favours bezafibrate

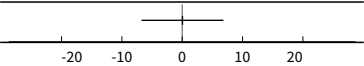
Analysis 6.4. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 4 Fasting serum triglyceride concentration (mmol/l).

Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	1.9 (0.5)	12	1.5 (0.8)		0.41[-0.12,0.94]

Favours bez with guar gum — Favours bezafibrate

Analysis 6.5. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 5 Fasting serum apolipoprotein A1 concentration (g/l).

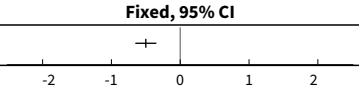
Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	1.2 (0.1)	12	1.2 (12)		0.04[-6.75,6.83]



Favours bez with guar gum — Favours bezafibrate

Analysis 6.6. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 6 Fasting serum apolipoprotein B-100 concentration (g/l).

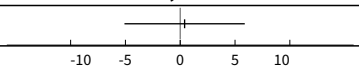
Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	1.6 (0.2)	12	2.1 (0.2)		-0.5[-0.65,-0.35]



Favours bez with guar gum — Favours bezafibrate

Analysis 6.7. Comparison 6 Dietary fibers as a form of dietary intervention compared to another form of dietary intervention or drug or no treatment, Outcome 7 Weight.

Study or subgroup	Bezafibrate with guar gum		Bezafibrate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Wirth 1982	12	72 (7.2)	12	71.6 (6.5)		0.4[-5.09,5.89]



Favours bez with guar gum — Favours bezafibrate

APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

#1 MeSH descriptor Dietary fiber explode all trees

#2 diet*

#3 MeSH descriptor Plant sterols explode all trees

#4 plant next sterol

#5 MeSH descriptor Plant stanol ester explode all trees

#6 stanol*

#7 MeSH descriptor Soy protein explode all trees

#8 Barley

#9 Guar gum

#10 Rice bran

11oat bran

12 rice bran

#13 flax seeds

#14 psyllium

#15 MeSH descriptor Omega 3 fatty acids explode all trees

#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#17 MeSH descriptor familial hypercholesterolemia explode all trees

#18 MeSH descriptor familial hyperlipoproteinemia explode all trees

#19 (#17 OR #18)

#20 (#16 AND #19)

WHAT'S NEW

Date	Event	Description
2 May 2014	New citation required but conclusions have not changed	Four new trials have been included in the update (Guardamagna 2011a; Ketomäki 2004a; Nigon 2001; Wirth 1982). Additional interventions (e.g. dietary fibers) have been added separately. No major changes have been made to the conclusions of the review.
2 May 2014	New search has been performed	A search of the Group's Inborn Errors of Metabolism Trials Regitser and PubMed identified four eligible trials for inclusion (Guardamagna 2011a; Ketomäki 2004a; Nigon 2001; Wirth 1982) which showed that the addition of plant sterols to the diet significantly reduced the total cholesterol, serum LDL and serum total triglycerides for patients with FH. The title has been changed from: Dietary treatment for familial hypercholesterolaemia.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 2, 2001

Date	Event	Description
20 September 2010	New search has been performed	Contact details updated. Three trials have been added to the previous update (Ketomäki 2004a, Guardamagna 2011a and Nigon 2001). The scientific statement from the American Heart Association (AHA) for the treatment of high-risklipid abnormalities in childr en and adolescents, which advocated the use of dietary treatment as adjuvant to pharmacolog ical treatment, was published in 2007. No revision of this statement has been published subsequently. F ollowing our updated review (2010), we are updating this review with additional information.
19 October 2009	New search has been performed	Four additional trials have been included in the current update (Engler 2004; Ketomäki 2003; Ketomäki 2005; O'Neill 2004); and three trials are listed as 'Awaiting classification' (Fuentes 2008; Retterstol 2009; Stein 2007).
19 October 2009	New citation required but conclusions have not changed	The team of review authors has changed. Vanessa Poustie and Patricia Rutherford are no longer active authors on this review. New comparisons between groups have been added. A previous comparison of cholesterol lowering diet and all other dietary interventions has been removed in the current update. Instead a new outcome for the evaluation of the effect of adding dietary intervention to drug therapy has been added in the present review.
31 October 2008	Amended	Converted to new review format.

Date	Event	Description
23 September 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

From 1999 to October 2008

The review authors were Vanessa Poustie and Patricia Rutherford. Each of these review authors participated in the writing of the text, the selection of eligible studies and the assessment of methodological quality. Vanessa Poustie undertook the searching for additional studies and extracted the data.

From October 2008:

Designing the review: Dr Nusrat Shafiq, Dr Meenu Singh Dr S. Malhotra
Data collection for the review: Dr Nusrat Shafiq
Designing search strategies: Dr Nusrat Shafiq, Natalie Yates (Trials Search Co-ordinator, Cochrane Cystic Fibrosis & Genetic Disorders Group)
Undertaking searches: Natalie Yates
Screening search results:Dr Nusrat Shafiq, Dr Pratibha Khosla, Dr Sharonjeet Kaur
Organising retrieval of papers: Natalie Yates
Screening retrieved papers against inclusion criteria:Dr Pratibha Khosla, Dr Nusrat Shafiq
Appraising quality of papers: Dr Pratibha Khosla, Dr Sharonjeet Kaur
Writing to authors of papers for additional information: Dr Nusrat Shafiq,Dr Meenu Singh
Obtaining and screening data on unpublished studies: Natalie Yates
Data management for the review: Dr Nusrat Shafiq, Dr Samir Malhotra, Dr Pratibha Khosla
Entering data into RevMan:Dr Nusrat Shafiq
Analysis of data: Dr Nusrat Shafiq, Dr Samir Malhotra
Interpretation of data:Dr Nusrat Shafiq, Dr Samir Malhotra, Dr Meenu Singh
Providing a methodological perspective:Dr Nusrat Shafiq, Dr Samir Malhotra
Providing a clinical perspective: Dr Nusrat Shafiq, Dr Meenu Singh, Dr Samir Malhotra,
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Writing the review: Dr Nusrat Shafiq, Dr Samir Malhotra
Providing general advice on the review: Dr Meenu Singh, Dr Samir Malhotra

From March 2012:

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Organising retrieval of papers: Natalie Yates and Ms. Neelima Chaddha
Screening retrieved papers against inclusion criteria: Dr Nusrat Shafiq and Dr. Anita Malhotra
Appraising quality of papers: Dr Nusrat Shafiq, Dr Anita Malhotra, Dr Samir Malhotra, Anjuman Arora, Rajendra Kumar
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Obtaining and screening data on unpublished studies: Natalie Yates
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DECLARATIONS OF INTEREST

None declared.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The comparisons listed in Objectives in the current update have been changed from the previous review, in line with the growing knowledge about the effects of dietary supplements in altering blood lipid levels.

May 2014: the title has been changed from 'Dietary treatment for familial hypercholesterolaemia'.

NOTES

The review was first published in Issue 2, 2001 by Vanessa Poustie and Patricia Rutherford. The review team changed to the current team from Issue 1, 2010.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Fat-Restricted; Cross-Over Studies; Fatty Acids, Omega-3 [administration & dosage]; Hyperlipoproteinemia Type II [*diet therapy]; Phytosterols [administration & dosage]; Randomized Controlled Trials as Topic; Soybean Proteins [administration & dosage]

MeSH check words

Adult; Child; Humans