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Low-fat diets for acquired hypercholesterolaemia (Review)

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[Intervention Review]

Low-fat diets for acquired hypercholesterolaemia

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ABSTRACT

Background

Hypercholesterolaemia, characterised by raised blood cholesterol levels, is not a disease itself but a metabolic derangement that often contributes to many diseases, notably cardiovascular disease. In most cases, elevated cholesterol levels are associated with high-fat diet, especially saturated fat, coupled with an inactive lifestyle. Less commonly, raised cholesterol may be related to an inherited disorder, familial hypercholesterolaemia. This systematic review is only concerned with acquired hypercholesterolaemia.

Objectives

To assess the effects of low-fat diets for acquired hypercholesterolaemia and to investigate the incidence of adverse effects from low-fat dietary interventions. We planned to compare the relative effectiveness of low-fat diets with calorie-restricted diets for acquired hypercholesterolaemia. We also wanted to look into the relative effectiveness of low-fat diets and pharmacological interventions for acquired hypercholesterolaemia.

Search methods

Studies were obtained from computerised searches of *The Cochrane Library,* MEDLINE, EMBASE and databases of ongoing trials. Date of last search was February 2010.

Selection criteria

Otherwise healthy adults (equal to or greater than 18 years) with acquired (not familial) hypercholesterolaemia. We defined hypercholesterolaemia as either total cholesterol greater than 5.2 mmol/L, LDL-cholesterol greater than 3.0 mmol/L, HDL-cholesterol less than 1.0 mmol/L or a combination thereof, although investigators' definitions were also accepted. We wanted to include any low-fat dietary intervention, like low-fat and low-saturated fat diets, intended to lower serum total and LDL-cholesterol or to raise HDL-cholesterol. A low-fat diet was considered as a fat calorie intake less than 20% of the total calories. The minimum duration of the intervention had to be six months. We excluded studies in unhealthy people.

Data collection and analysis

Two authors were planned to independently assess risk of bias and extract data.

Main results

No study met our inclusion criteria.

Authors' conclusions

Well designed, adequately powered randomised controlled trials investigating patient-relevant outcomes of low-fat diets for otherwise healthy people with hypercholesterolaemia are required.

PLAIN LANGUAGE SUMMARY

Low-fat diets for acquired hypercholesterolaemia

There is currently no firm evidence of the long-term (at least six months) effects of low-fat diets for otherwise healthy people with acquired, that is not familial hypercholesterolaemia (high cholesterol levels in the blood). Various low-fat diets have been investigated in people with long-term illnesses, however, a high quality trial of at least six months duration in otherwise healthy people with high blood cholesterol is needed.

BACKGROUND

Description of the condition

Hypercholesterolaemia, characterised by raised blood cholesterol levels, is not a disease itself but a metabolic derangement that can be secondary and often contributes to many diseases, most notably cardiovascular disease (CVD). In most cases, elevated cholesterol levels are associated with a diet high in fat, especially saturated fat, coupled with an inactive lifestyle. Less commonly, raised cholesterol may be related to an inherited disorder, familial hypercholesterolaemia. This systematic review is only concerned with acquired hypercholesterolaemia.

Hypercholesterolaemia is often associated with raised levels of low-density lipoprotein (LDL), a type of lipoprotein that transports cholesterol and triglycerides from the liver to peripheral tissues. LDL also regulates cholesterol synthesis at these sites. Hypercholesterolaemia is likely to also be associated with low levels of high-density lipoproteins (HDL), another type of lipoprotein which enable lipids like cholesterol and triglycerides to be transported within the blood stream. HDL can remove cholesterol from atheroma within arteries and transport it back to the liver for excretion or re-utilization. Hypercholesterolaemia can increase a person's risk of cardiovascular disease via the intermediate step of plaque creation along artery walls, or atherosclerosis. Plaques can eventually obstruct or even block the flow of blood to the brain, heart, and other organs, which in turn can lead for example to stroke or heart attack. Atherosclerosis is a chronic inflammatory response in the walls of the arteries, which largely is due to the accumulation of white blood cells called macrophages. Atherosclerosis is promoted by LDL, when there is inadequate removal of fats and cholesterol from the macrophages by functional HDL, leading to the formation of multiple plaques within the arteries.

Atherosclerosis, though typically asymptomatic for years, eventually produces two main problems. The first problem is when plaques rupture, and clots form inside the artery lumen over the ruptures. The clots heal and usually shrink but leave behind stenosis of the artery, or worse, complete closure, and therefore, an insufficient blood supply to the tissues and organ it feeds. The second problem is when aneurysm results, due to the excessive enlargement process of the compensating artery. These complications of advanced atherosclerosis are chronic, slowly progressive and cumulative. Most commonly, soft plaque suddenly ruptures causing the formation of a thrombus that will rapidly slow or stop blood flow, leading to an infarction, hence leading to heart attack or stroke.

The link between hypercholesterolaemia and cardiovascular disease is equivocal with extrapolations from cardiovascular risk factor statistics to atherosclerosis deemed questionable in some cases (Stehbens 2001). It has been postulated that atherosclerosis is an inflammatory process which may explain inconsistencies between risk factors and disease prevalence and severity. Some of the cholesterol-independent effects of statins involve improved endothelial function, stability of atherosclerotic plaques, attenuation of oxidative stress and inflammation, as well as inhibition of the thrombogenic response (Athyros 2009). Evidence suggests that in high CVD risk patient groups pleiotropic effects of statins (see below) may play a role in the reduction of morbidity and mortality. However, this concept requires proof in appropriately designed trials that will include clinically relevant end points in order to set specific targets in new CVD-related bio markers, in addition to lipid levels, that should be used to fully assess the statin contribution to CVD treatment (Athyros 2009). In contrast, other works cite

moderately good correlation between dietary saturated fatty acids and coronary heart disease (CHD) when populations in different parts of the world are compared, although this may not be true within the same cultural community or for individuals (Oliver 1982). Total energy, essential fatty acids (EFA), dietary fibre, alcohol and salt also contribute to the relationship of diet to CHD. Saturated fatty acids exert their pathogenic role mostly through altering the homoeostasis of lipoprotein metabolism, leading to an increase in cholesterol-rich low-density lipoproteins, and influencing adversely the balance between the accumulation in and clearance of cholesterol esters from the arterial wall. Polyunsaturated fatty acids (PUFA) alter lipoprotein metabolism directly by decreasing synthesis and increasing catabolism and excretion and indirectly by being substitutes for saturated fatty acids, which are therefore consumed in smaller quantities (Oliver 1982). In summary, normal or raised levels of HDL seem to protect against cardiovascular diseases, whereas low HDL-cholesterol levels seem to increase the risk for heart disease, although other dietary and environmental factors and inter-individual variations also affect the rate of atherosclerotic disease progression.

Prevalence and burden

For over 50 years physicians have been aware that the aetiology of atherosclerosis is usually hypercholesterolaemia (Pollak 1953). The prevalence of hypercholesterolaemia in US adults is estimated to be between 37% and 55% (Ford 2003). According to US data the leading cause (over 60%) of all mortalities in 2002 were due to cardiovascular disease, equating to over 700,000 deaths annually (Callow 2005). A study of 7640 patients estimated total disease-related costs, related to objective hypercholesterolaemia to be a mean of EUR 2498 to 4898 (USD 3229 to 6332) per patient over six months, comprising direct (44%) and indirect (56%) costs (Muller-Nordhorn 2008). Other disease-related burdens like early retirement were responsible for 42% of costs, followed by hospital visits (19%), medication (15%), workdays lost (14%), physician visits (5%), outpatient therapy (2%), and rehabilitation (2%).

Diagnosis and treatment targets

Diagnosis and treatment of hypercholesterolaemia is based on blood measurements or estimations (Friedwald formula estimates LDL, Niedbala 1985) of at least three different fractions of cholesterol; total cholesterol (TC), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL). The following Table 1 demonstrates how treatment targets for TC, LDL and HDL differ slightly in European (De Backer 2004) and Australian (Tonkin 2005) guidelines.

Description of the intervention

It is recommended that first line treatment for hypercholesterolaemia entails dietary and 'lifestyle' modification. Examples of lifestyle interventions are diets that place daily limits on total energy, fat, saturated fat, cholesterol (usually less than 200 mg per day); increased consumption of soluble fibre and inclusion of two grams of plant sterols/stanols per day in addition to a program of physical activity (De Backer 2004; National Cholesterol Education Program 2002; Tonkin 2005; Varady 2005). As excess energy intake will lead to weight gain via fat storage all low-fat diets by definition require total energy restriction. Most low-fat diets also restrict the proportion (percentage) of calories obtained from fat and in some cases restrictions are placed on proportion of calories obtained from saturated fat also (low saturated fat diets). Furthermore, it is widely accepted that patients should be advised to increase their intake of essential fatty acids of marine origin, n-3 eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) due to their potential protective effect against cardiovascular disease (WHO 2003).

A meta-analysis of studies revealed that replacement of 60% of calories from saturated fats with a combination of polyunsaturated fats and monounsaturated fats resulted in falls in total cholesterol of 0.8 mmol (10% to 15%), with this reduction being primarily LDL-cholesterol (Clarke 1997). Moreover, studies measuring the effects of plant sterols and stanols on cholesterol have demonstrated that the mean LDL reduction was approximately 12% (Noakes 2002) and on average, an increase in soluble fibre of 510 grams per day is accompanied by an approximately 5% reduction in LDL-cholesterol (National Cholesterol Education Program 2002). Moreover, a systematic review reported small but potentially important reductions in cardiovascular risk (rate ratio 0.84, 95% confidence interval (CI) 0.72 to 0.99) with reduction or modification of dietary fat intake, seen particularly in trials of longer duration (Hooper 2000).

The combined effects of step 1 and 2 dietary interventions (see below) can potentially result in a decrease in total cholesterol in the order of up to 30% (Yu-Poth 1999). However, if after a period of 3 to 6 months lifestyle modification is deemed ineffective or has not effected desired treatment goals (see Table 1) then lipid-lowering medications may be prescribed. The first-line pharmacotherapy for hypercholesterolaemia is a HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor or 'statin'. Statins lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Inhibition of this enzyme in the liver stimulates LDL receptors, resulting in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels. The first results can be seen after one week of use and the effect is maximal after 4 to 6 weeks. If possible, it is preferable to avoid statin therapy as there are in some cases side-effects, cost-implications, compliance is poor (Liberopoulos 2008) and targeting of statins at low-risk populations is associated with major uncertainties (Ward 2007). Dietary interventions may look as follows:

- Step 1 diet of the American Heart Association or its equivalent (less than 30% of total energy intake as fat, with 8% to 10% as saturated fat; ratio of polyunsaturated to saturated fatty acid greater than 1.0; cholesterol intake less than 300 mg/day; and energy intake to achieve desirable body weight).
- Step 2 diet of the American Heart Association or its equivalent (less than 30% of total energy intake as fat, with 7% or less as saturated fat; ratio of polyunsaturated to saturated fatty acid greater than 1.4; cholesterol intake less than 200 mg/day; and energy intake to achieve desirable body weight).

How the intervention might work

Blood cholesterol is related to dietary intake of saturated fat, so if saturated fat intake is restricted blood cholesterol levels should fall. A meta-analysis by Clarke et al (Clarke 1997) reported that for each 1% increase in energy from saturated fats, serum LDL-cholesterol will increase between 0.33 mmol/L and 0.45 mmol/L. Several large, well-designed, randomised controlled drug trials have established that effectively treating hypercholesterolaemia may retard or prevent cardiovascular disease (Pederson 1998; WOSCOPS 1996), however pleiotropic effects of statins suggest that alternate mechanisms (than only lowering plasma cholesterol) such as, stabilising plaques and attenuating oxidative stress and inflammation, may also have a role (Athyros 2009). The Scandinavian Simvastatin Survival Study reported that cholesterol lowering with simvastatin reduced the incidence of carotid bruits and cerebrovascular events as well as new-onset or worsening of angina pectoris and intermittent claudication (Pederson 1998). A Cochrane systematic review has suggested small but potentially important reductions in cardiovascular risk in dietary intervention trials longer than two years are possible in those at high risk of cardiovascular disease (especially where statins are unavailable or rationed). Moreover, lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by un-saturates (Hooper 2000). We therefore wish to examine if via the intermediate step, of reducing cholesterol levels by low-fat diet, there may be positive effects on cardiovascular outcomes.

Adverse effects of the intervention

Adverse effects are rare but an excessive rate of weight loss can result in muscle wasting and deficiencies in vitamins and minerals as well as possible psychological side-effects.

Why it is important to do this review

The review is important as natural or non-pharmacological solutions to most chronic diseases and metabolic derangements, hypercholesterolaemia included, are preferred as side-effects of pharmacological therapy present health risks. Overweight, obesity, cardiovascular, renal disease and diabetes have reached global epidemic proportions and are related to hypercholesterolaemia and significantly raised risk of morbidity and mortality. Therefore, the importance of treating hypercholesterolaemia is great and potential benefits exist.

A Cochrane systematic review of dietary advice for reducing cardiovascular risk reported modest reductions in TC and LDL-cholesterol (Brunner 2007). Another systematic review evaluated various dietary and pharmacological interventions for reducing mortality (Struder 2005). A 1999 meta-analysis evaluated the effects of the National Cholesterol Education Program's step 1 and step 2 dietary interventions on major cardiovascular disease risk factors (National Cholesterol Education Program 2002). This analysis found that plasma TC, LDL-cholesterol, triacylglycerol, and TC: HDL-cholesterol decreased by 0.63 mmol/L (10%), 0.49 mmol/L (12%), 0.17 mmol/L (8%), and 0.50 mmol/L (10%), respectively, in step 1 intervention studies ($P < 0.01$ for all). As no recent systematic review has looked at isolated effects of low-fat (step 1) diets, for lowering cholesterol profiles and other effects, this is the primary focus of our work.

OBJECTIVES

To assess the effects of low-fat diets for acquired hypercholesterolaemia.

To compare the relative effectiveness of low-fat diets with calorie-restricted diets for acquired hypercholesterolaemia.

To compare the relative effectiveness of low-fat diets and pharmacological interventions for acquired hypercholesterolaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials.

Types of participants

Otherwise healthy adults (equal to or greater than 18 years) with acquired (not familial) hypercholesterolaemia. The preferred definition of hypercholesterolaemia was either total cholesterol greater than 5.2 mmol/L, LDL-cholesterol greater than 3.0 mmol/L, HDL-cholesterol less than 1.0 mmol/L or a combination thereof, although other definitions were accepted. Studies of familial hypercholesterolaemia were excluded. Changes in diagnostic criteria

could produce significant variability in the clinical characteristics of the patients included as well as in results obtained. These differences were planned to be considered and explored in a sensitivity analysis.

Types of interventions

The minimum duration of the intervention had to be six months.

Intervention

Any low-fat dietary intervention (e.g. low-fat and low-saturated fat diets) intended to lower serum total or LDL-cholesterol or to raise HDL-cholesterol.

Control

Usual care, calorie-restricted diets or pharmacological interventions.

Types of outcome measures

Primary outcomes

- blood lipids (serum total cholesterol, LDL- and HDL-cholesterol);
- cardiovascular events (e.g. myocardial infarction, stroke);
- death from any cause.

Secondary outcomes

- adverse effects;
- health-related quality of life;
- healthcare costs;
- serum triglyceride concentration (fasting and non-fasting).

Covariates, effect modifiers and confounders

- gender;
- age.

Timing of outcome measurement

Minimum duration of outcome assessment had to be six months, meaningful time points were one year, two years and five years. We planned to clearly separate length of follow-up from treatment duration. We also wanted to consider length of follow-up under randomised and non-randomised conditions.

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- The *Cochrane Library* (Issue 1, 2010);
- MEDLINE (until February 2010);
- EMBASE (until February 2010).

We also searched databases of ongoing trials:

- Current Controlled Trials (http://www.controlled-trials.com - with links to other databases of ongoing trials)
- UK National Research Register (http://www.update-software.com/National/)
- USA - CenterWatch Clinical Trials Listing Service (http://www.CenterWatch.com/)
- USA - National Institutes of Health (http://clinicalstudies.info.nih.gov/)

For detailed search strategies please see under Appendix 1. Additional key words of relevance could have been detected during the electronic or other searches. If this was the case, electronic search strategies would have been modified to incorporate these terms. We planned to include studies published in any language.

Searching other resources

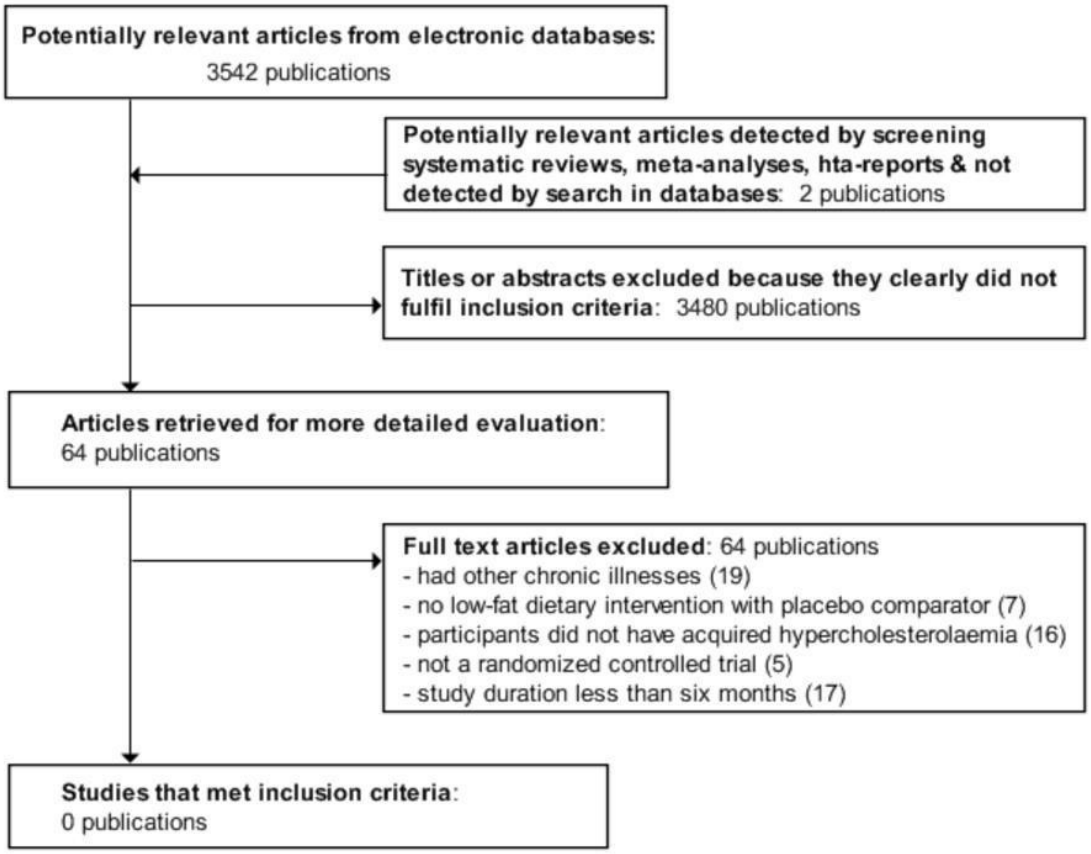
We planned to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports noticed.

Data collection and analysis

Selection of studies

A flow-chart of the number of studies (Figure 1) identified and excluded at each stage was prepared in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati 2009). The flow-chart was applied by two authors (EB and JW) and inter-rater agreement was 100% (Cohen 1960), differences in opinion would have been resolved by a third author (NS) by consensus. We did not plan to blind trials for trial selection and risk of bias assessment.

Figure 1. Adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of study selection



Data extraction and management

Data extraction tables were planned to be used according to the template provided by the Cochrane Metabolic and Endocrine Disorders Review Group. Both data extraction and entry was to be done in duplicate by two authors, LM and EB. Differences in data extraction would have been resolved by consulting a third person (NS) and referring back to the original paper. We wanted to contact authors of identified papers about duplicate studies, missing information in their trials, e.g. methods of randomisation and allocation concealment, separate information for certain patient subgroups, information about complications etc.

Assessment of risk of bias in included studies

We planned to perform risk of bias assessment in duplicate by two authors BM and CE using the Cochrane Collaboration's risk of bias tool (Higgins 2008). We wanted to report inter-rater agreement using Cohen's kappa (Cohen 1960) on key quality issues (like concealment of allocation) and differences in opinion would have been resolved by consulting a third author (NS).

Measures of treatment effect

Dichotomous data

Dichotomous outcomes (for example stroke yes/no) would have been expressed as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI). Odds ratios were planned to be reported in analysed studies if event rates were less than 10%.

Continuous data

Continuous outcomes (for example LDL-cholesterol) were planned to be expressed, if possible, as mean differences with 95%

CI. We intended to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Time-to-event data

Time-to-event outcomes (for example time until death) were planned to be expressed as hazard ratios (HR) with 95% CI.

Unit of analysis issues

We planned to exclude data from cluster-randomised trials.

Dealing with missing data

Relevant missing data would have been obtained from authors, if feasible. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat and per-protocol population would have been carefully performed. Attrition rates like drop-outs, misses to follow-up and withdrawn study participants were planned to be investigated. Issues of last-observation-carried-forward (LOCF) would have been critically appraised and compared to specification of primary outcome parameters and power calculation.
In the case of duplicate publications and companion papers of a primary study, we intended to try to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) would have obtained priority.

Assessment of heterogeneity

We planned to investigate heterogeneity irrespective of whether it was statistically significant or not. If appropriate, causes of heterogeneity may be subdivided into five domains:

- the patient (for example rate of drug metabolism, risk factors, co-morbidity, compliance);
- the disorder (for example stage of development, duration);
- the intervention (for example doses, routes, timing, study design factors);
- the comparison (for example different control interventions, co-medication);
- the outcome (for example timing of measurement, method of measurement).

In the event of substantial clinical or methodological or statistical heterogeneity, we did not intend to combine study results by means of meta-analysis. Heterogeneity would have been identified by visual inspection of the forest plots, by using a standard Chi^2 test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity would have been specifically examined with the I^2 statistic (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003).
In case heterogeneity was detected, we planned to attempt to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

Funnel plots would have been used to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies and publication bias (Sterne 2001). Therefore, we would have carefully interpreted findings (Lau 2006).

Data synthesis

Data were planned to be summarised statistically if available, sufficiently similar and of sufficient quality. Statistical analysis would have been performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2008).

Method of meta-analysis

We planned to use the Mantel-Haenzel fixed-effect model, reporting odds ratios and 95% confidence intervals. In order to contrast absolute and relative measures, we also wanted to express results as number-needed-to-treat (to benefit or to harm) (NNTB, NNTH). NNTB and NNTH depend among other things upon follow-up time and baseline risk. We therefore planned to adjust for follow-up time by annualising NNTH and NNTB as described previously (Mayne 2006). For discrete data we planned to adjust for baseline risk by analysing change in event rates, for continuous data if groups were not matched at baseline we intended to only report descriptively.

Expression of results

We aimed to express results in a way that is easily comprehensible to the reader. We wanted to use a combination of underlying event rates, expressing results as NNTB and NNTH adjusted for follow-up time and baseline risk.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to determine whether there were any systematic differences between groups of patients. Examples of possible subgroup analyses are: stratification by age, sex, different comparison interventions, different follow-up duration. In each subgroup analysis the groups were planned to be clearly defined. We wanted to avoid subgroup analyses if there was no statistically significant treatment effect in one of our primary outcomes.
The following subgroup analyses were planned:

- analyses of patients with and without co-morbid conditions, e.g. diabetes, cardiovascular disease, obesity.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- use of non-validated measurement scales or tools;
- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results would have been tested by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed-effect model and random-effects model).

RESULTS

Description of studies

The search identified 3544 publications, 64 articles were excluded after full text evaluation (Figure 1). For description of excluded studies, please see table Characteristics of excluded studies.

Risk of bias in included studies

No study met our inclusion criteria.

Effects of interventions

No study met our inclusion criteria.

DISCUSSION

No study met our inclusion criteria.

Sub-optimal management of hypercholesterolaemia has potentially huge global health and economic burdens. Often those newly diagnosed with hypercholesterolaemia will be advised to follow a low-fat diet. Our initial search for studies of low-fat diets to manage isolated hypercholesterolaemia, in otherwise healthy people, revealed no studies that met our inclusion criteria. The main reasons for exclusion were that studies were often in either mixed populations (those with and without hypercholesterolaemia, or those with and without cardiovascular disease) so the effect of isolated hypercholesterolaemia could not be quantified. Other studies were excluded because they were not of insufficient duration (less than six months) to reasonably expect a cholesterol lowering effect. Other excluded studies were either combined interventions, for example drugs plus low-fat diets or were studies undertaken in individuals concurrently taking cholesterol lowering medication, so the effects of low-fat diets could not be isolated. We were therefore unable to draw conclusions whether the isolated effects of low-fat diets are effective in managing isolated hypercholesterolaemia. As uncontrolled hypercholesterolaemia has significant global health and economic implications, adequately designed randomised, controlled trials are required to guide clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Many physicians and allied health practitioners advise people with hypercholesterolaemia to undertake a low-fat diet. Additionally many people may 'self-treat' by placing themselves on low-fat diets. In both these scenarios the treatment goal can be to manage or lower patients' blood cholesterol levels. Our review has illustrated that no firm published evidence exists to support the widely held opinion that low-fat diets will in fact lower blood cholesterol levels.

Implications for research

This review provides significant implications for research, as no randomised, controlled study of low-fat dietary intervention versus usual care, of at least six months duration in healthy people, has been published to date.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Aquilani 1999	Participants had other chronic disease at baseline
Avogaro 1983	Not low fat dietary intervention (fibrate trial)
Baumann 1982	Not low-fat diet versus placebo (niacin)
Birley 1997	Participants did not have acquired hyperlipidaemia
Blacket 1979	Participants did not have acquired hyperlipidaemia
Bowen 1996	Not a randomised controlled trial
Boyd 1996	Participants did not have acquired hyperlipidaemia
Bravo-Herrera 2004	Study less than six months duration
Brehm 2003	Participants had other chronic disease at baseline
Brown 1984	Participants had other chronic disease at baseline
Carmena 1984	Participants did not have acquired hyperlipidaemia
Cortese 1983	Study less than six months duration
Davidson 1998	Study less than six months duration
de Bont 1981	Participants had other chronic disease at baseline
Dengel 1994	Not a randomised controlled trial
Due 2008	Not low fat dietary intervention (post weight-loss trial)
Fagerberg 1998	Participants had other chronic disease at baseline
Fernandez 2002	Study less than six months duration
Fleming 2002	Participants did not have acquired hyperlipidaemia
Gonzalez 1996	Study less than six months duration
Gordon 1982	Participants did not have acquired hyperlipidaemia

(*Continued*)

Gosselin 1996	Participants had other chronic disease at baseline
Hannah 1997	Study less than six months duration
Haugaard 2009	Study less than six months duration
Hjermann 1980	Participants had other chronic disease at baseline
Hutchinson 1983	Participants had other chronic disease at baseline
Hyman 1998	No dietary intervention, no measure of dietary effects
Jenkins 1993	Study less than six months duration
Jenkins 1999	Study less than six months duration
Jenkins 2009	Participants had other chronic disease at baseline
Judd 1988	Study less than six months duration
Kuo 1976	Participants did not have acquired hyperlipidaemia
Kuo 1978	Participants did not have acquired hyperlipidaemia
Lantz 2003	Study less than six months duration
Lewis 1981	Study less than six months duration
Liu 1984	Study less than six months duration
MacMahon 1998	Participants did not have acquired hyperlipidaemia
Marckmann 1998	Participants did not have acquired hyperlipidaemia
Mellies 1987	Not dietary intervention, no measure of dietary effects
Miida 1998	Study less than six months duration
Mishra 1994	Not a randomised, controlled trial
Muller 2000	Participants had other chronic disease at baseline
Nessim 1983	Participants did not have acquired hyperlipidaemia
Nicklas 2003	Participants had other chronic disease at baseline
Niebauer 1995	Participants had other chronic disease at baseline

(*Continued*)

Niebauer 1997	Participants had other chronic disease at baseline
O'Bryne 1998	Study less than six months duration
O'Byrne 1997	Not a randomised controlled trial
Oh 1985	Participants did not have acquired hyperlipidaemia
Paisey 1995	Participants had other chronic disease at baseline
Reuter 1984	Participants did not have acquired hyperlipidaemia
Schaefer 1981	Study less than six months duration
Shai 2008	Participants had other chronic disease at baseline
Shikany 2005	Study less than six months duration
Shorey 1976	Participants did not have acquired hyperlipidaemia
Tapsell 2004	Participants had other chronic disease at baseline
Turner 1981	Participants had other chronic disease at baseline
Vidgren 1999	Not dietary intervention (statin trial)
Wass 1981	Participants had other chronic disease at baseline
Williams 1994	Not exclusive dietary intervention (secondary intervention was employed)
Wolfe 1995	Not a randomised controlled trial
Wood 1991	Participants did not have acquired hyperlipidaemia
Yancy 2004	Participants had other chronic disease at baseline
Zambon 1999	Participants did not have acquired hyperlipidaemia

ADDITIONAL TABLES

Table 1. Primary treatment targets for blood lipids

Guidelines	Total cholesterol		HDL-C		LDL-C	
ESC (De Backer 2004)	General	< 5.0 mmol/L (< 190 mg/dL)	Women	> 1.2 mmol/L (> 45 mg/dL)	General	< 3.0 mmol/L (< 115 mg/dL)
	High risk[a]	< 4.5 mmol/L (< 175 mg/dL)	Men	> 1.0 mmol/L (> 40 mg/dL)	High risk	< 2.5 mmol/L (< 100 mg/dL)
NHF (Tonkin 2005)	General	< 5.5 mmol/L (< 210 mg/dL)	> 1.0 mmol/L (> 40 mg/dL)	General	< 3.0 mmol/L (< 115 mg/dL)	
	High risk[a]	< 4.0 mmol/L (< 155 mg/dL)	> 1.0 mmol/L (> 40 mg/dL)	High risk[a]	< 2.5 mmol/L (< 100 mg/dL)	

[a] High risk indicates that the patient has other risk factors for cardiovascular disease which may include age, smoking, metabolic syndrome.

ESC: European Society of Cardiology; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NHF: National Heart Foundation (Australia)

APPENDICES

Appendix 1. Search strategies

Search terms
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent
The Cochrane Library, Issue 1.2010
#1 MeSH descriptor Hypercholesterolemia explode all trees
#2 MeSH descriptor Hyperlipidemias explode all trees
#3 MeSH descriptor Cholesterol, HDL explode all trees
#4 MeSH descriptor Cholesterol, LDL explode all trees
#5 hypercholester* in All Text
#6 hyperlipid?emia* in All Text
#7 hyperlip?emia* in All Text
#8 (high in All Text and density in All Text and lipoprotein in All Text and cholesterol* in All Text)
#9 HDL-C in All Text
#10 (low in All Text and density in All Text and lipoprotein in All Text and cholesterol* in All Text)
#11 LDL-C in All Text

(*Continued*)

#12 (total in All Text and cholesterol* in All Text)
#13 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14 MeSH descriptor Diet therapy explode all trees
#15 MeSH descriptor Diet, Fat-Restricted explode all trees
#16 (diet* in All Text near/6 fat* in All Text)
#17 (#14 or #15 or #16)
#18 (#13 and #17)
#19 MeSH descriptor Adult explode all trees
#20 adult* in All Text
#21 (#19 or #20)
#22 (#18 and #21)

MEDLINE (until February 2010)
1. exp Hypercholesterolemia/
2. exp Hyperlipidemias/
3. exp Cholesterol, HDL/
4. exp Cholesterol, LDL/
5. Hypercholester$.ab,ti,ot.
6. hyperlipid?emia$.ab,ti,ot.
7. hyperlip?emia$.ab,ti,ot.
8. high density lipoprotein cholesterol$.ab,ti,ot.
9. HDL-C.ab,ti,ot.
10. low density lipoprotein cholesterol$.ab,ti,ot.
11. LDL-C.ab,ti,ot.
12. total cholesterol$.ab,ti,ot.
13. or/1-12
14. exp Diet Therapy/
15. exp Diet, Fat-Restricted/
16. (diet$ adj6 fat$).ab,ti,ot.
17. or/14-16
18. 13 and 17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. drug therapy.fs.
24. randomly.ab.
25. trial.ab.
26. groups.ab.
27. or/19-26
28. Meta-analysis.pt.
29. exp Technology Assessment, Biomedical/
30. exp Meta-analysis/
31. exp Meta-analysis as topic/
32. hta.tw,ot.
33. (health technology adj6 assessment$).tw,ot.
34. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
35. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current

content$ or systemat$)).tw,ot.
36. or/28-35
37. 27 or 36
38. 18 and 37
39. limit 38 to "all adult (19 plus years)"

EMBASE: (until February 2010)
1. exp Hypercholesterolemia/
2. exp Hyperlipidemia/
3. exp High Density Lipoprotein Cholesterol/
4. exp Low Density Lipoprotein Cholesterol/
5. hypercholester$.ab,ti,ot.
6. hyperlipid?emia$.ab,ti,ot.
7. hyperlip?emia$.ab,ti,ot.
8. high density lipoprotein cholesterol$.ab,ti,ot.
9. HDL-C.ab,ti,ot.
10. low-density lipoprotein cholesterol$.ab,ti,ot.
11. LDL-C.ab,ti,ot.
12. exp Cholesterol Blood Level/
13. total cholesterol$.ab,ti,ot.
14. or/1-13
15. exp Diet Therapy/
16. exp Low Fat Diet/
17. (low fat diet$ or restricted fat diet$).ab,ti,ot.
18. or/15-17
19. 14 and 18
20. random$.tw.
21. (crossover$ or cross over$).tw.
22. (double adj blind$).tw.
23. (single adj blind$).tw.
24. (assign$ or allocat$ or volunteer$).tw.
25. Crossover Procedure/
26. Double Blind Procedure/
27. Randomized Controlled Trial/
28. Controlled Clinical Trial/
29. Single Blind Procedure/
30. Randomization/
31. or/20-30
32. exp meta analysis/
33. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
34. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current
content$ or systematic$)).ab,ti,ot.
35. exp Literature/
36. exp Biomedical Technology Assessment/
37. hta.tw,ot.
38. (health technology adj6 assessment$).tw,ot.
39. or/32-38
40. 31 or 39

(*Continued*)

41. 19 and 40
42. limit 41 to (adult <18 to 64 years> or aged <65+ years>)

CONTRIBUTIONS OF AUTHORS

NEIL SMART: Edited the protocol and verified included/excluded studies.

ELIE BOULOS: Assisted with writing the protocol.

NIGEL KWOK: Assisted with writing the protocol.

BELINA J MARSHALL: Provided dietary advice with regard to the background and protocol, classified studies to be included/excluded, assisted with report writing.

NADINE BAKER: Provided dietary advice with regard to the background and protocol, classified studies to be included/excluded, assisted with report writing.

MAXINE DALEY: Provided dietary advice with regard to the background and protocol, classified studies to be included/excluded, assisted with report writing.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Diet, Fat-Restricted [adverse effects; *methods]; Hypercholesterolemia [*diet therapy]

MeSH check words

Adult; Humans