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Supplemental plant sterols and stanols for serum cholesterol and cardiovascular disease

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To determine the effects of phytosterols, phytostanols or their esters, ingested in supplemented foods, on blood cholesterol concentrations and cardiovascular disease;
2. To look for adverse effects e.g. on nutritional status or physiological function;
3. To study/comment on, possible effects of cost.

BACKGROUND

Cholesterol is the principal lipid, circulating in the blood, that is associated with atherosclerosis and coronary heart disease. Triglycerides, particularly saturated fats, are also implicated.

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CONTRIBUTIONS OF AUTHORS Mr David Potter. Conceived the review, prepared first draft of protocol (excluding Search Strategy, Methods and Data Synthesis) and coordinated development of protocol. Will participate in and coordinate development of review. Will screen papers for inclusion / exclusion, extract data and designate quality. Will help analyse data and interpret results. Dr Lee Hooper. Completed the first draft of the protocol and co-developed it. Made input to Search Strategy. Will participate in development of the review, screen papers for inclusion/exclusion, extract data and designate quality. Will help analyse data and interpret results.

Ms Margaret Burke. Developed Search Strategy. Reviewed, commented on and approved protocol. Will retrieve papers of interest and will progress quantitative recovery of reports of relevant trials.

Mrs Pauline Rigby is new to Cochrane systematic reviewing. However, she is an experienced reviewer of nutritional research. She is keen to participate and her input will be developed with the review.

Prof Carolyn Summerbell. Reviewed, commented on and approved protocol.

Mrs Vicki Whittaker. Will advise on methodology and supervise statistical analysis of results. Will help analyse data and interpret results.

DECLARATIONS OF INTEREST David Potter uses Benecol products and Flora Proactive spread with the intention of lowering his blood cholesterol concentration. The fact that he uses these products rather than the regular spreads etc. which are significantly cheaper, indicates that he believes that they may work.

The co-reviewers are aware of Mr Potter's bias and will offer counterbalancing views. Further, all reviewers are aware that much of the evidence for the effectiveness of stanols and sterols is likely to have been generated by individuals and organisations with a financial interest in the success of the product.

Atherosclerosis is caused by the deposition of cholesterol in the artery walls causing them to thicken, become narrower and less elastic, thus impairing their function. When this occurs in vital arteries supplying blood to the heart it leads to coronary heart disease by reducing the flow of blood and hence also the supply of nutrients and oxygen vital for proper heart function.

Most of the cholesterol in the body is manufactured there. It is made in all organs of the body but principally the liver and intestine. It is essential to our good health because it has a vital role in the structure of cell membranes, is made into steroid hormones (which have a role in every aspect of normal body function) and is made into bile salts. In the healthy adult on a “normal” varied diet about 0.4 grams per day of cholesterol will be eaten, but 1 gram of cholesterol per day is produced by the body. Cholesterol, in the form of esters and bile salts, is a component of bile, which is released into the intestine to aid the digestion of fats. Most of it is then re-absorbed from the intestine into the body. Thus, it is estimated that a relatively small pool of bile acid (3-5g) is cycled through the intestine 6-10 times per day with a loss of only 1-2% per pass (Mayes 2000). Cholesterol is transported in the blood in association with “high density lipoprotein” (HDL) and “low density lipoprotein” (LDL). It is the concentration of LDL cholesterol that has been correlated with increased risk of cardiovascular disease.

Plant sterols and stanols, ingested in our food, are thought to reduce the level of cholesterol in the blood. Proposed mechanisms suggest that they dilute the pool of cholesterol in the intestine and compete with cholesterol for the available absorption capacity (IFST 2000). This is because of their chemical (e.g. molecular structure) and physical (e.g. solubility) similarity to cholesterol. They are absorbed to a lesser extent than cholesterol, only about 5% of phytosterols and phytostanols being absorbed in humans (Heinemann 1993). The exact mechanism is not known. It is claimed that the same reduction in blood cholesterol can be achieved whether the daily recommended intake is achieved at one meal or spread over the day e.g. 3 meals (Katan 2003). This and relatively low absorption of the phytosterols compared to cholesterol, suggest that the effect might be mediated through an enzyme or transporter protein in the following way: Small molecules like cholesterol bind to larger protein molecules because of their shape that fits into a complimentary pocket in the protein, a bit like a key in a lock. Phytosterols and phytostanols, which are similar in shape to cholesterol, bind to the same sites, but more strongly because of their slightly different structure and thus chemistry. This effectively reduces the number binding sites on the protein available to cholesterol molecules.

The prefix “phyto-”, meaning plant, will be used throughout this review. Thus, “phytosterols” are found in all plants as the free sterol and as conjugates (attached to another substance such as glucose, when they are called “glycosides”, or to fatty acids, when they are called “esters”). Their function in plants is similar to that of cholesterol in animals, that is they play an important role in the structure and function of cells (Moreau 2002).

Experiments in the 1950s first showed that eating relatively pure phytosterols extracted from plants could reduce the level of cholesterol in the blood (Pollak 1953). At that time the ‘sitosterol’ mixture used was unpalatable. The difficulties of formulating stanols and sterols

in a way that made them palatable and consistently effective were problems that made them unacceptable as supplements for several decades (although sitosterol was sold as a lipid lowering agent in the 1950s, later replaced by the more predictable statin drugs (Moreau 2002)). The levels of phytosterols in plants are low, so that we ingest about 0.2 to 0.4 g per day in our normal diet, and “phytosterols” occur in plants at even lower concentrations (IFST 2000). So, they have to be extracted from plants and concentrated for use as dietary supplements. The effects of supplemental phytosterols and phytosterols on blood cholesterol levels have been investigated in high dose (up to 25g/day) clinical trials, involving more than 1800 people (Pollak 1981). Esterification, the attachment of phytosterols to fatty acids by chemical reaction, improved their solubility and lead to clinical trials to investigate the effects of dietary spreads supplemented with phytosterols and phytosterols (Hendriks 1999), as well as marketing of these products. They are formulated at concentrations that will provide a dose of 1 - 2 g per day in 25 g of spread (IFST 2000).

In the UK, supplementary sterols are available as formulations in a margarine spread, whereas the related stanols are available in margarine or cottage cheese style spreads, in yoghurt and in a cereal bar.

A potential harm associated with use of phytosterols and phytosterols is the reduction of plasma beta-carotene and lycopene levels, probably due to reduced absorption of fat-soluble vitamins and carotenoids as well as cholesterol (Weststrate 1998). As carotenoids are associated with positive health benefits their reduction may be a cause for concern. Other side effects associated with use of beta-sitosterol have been anorexia, cramping and diarrhoea (Meyler's 1988), plus gastrointestinal disturbances (in 2.5% of people taking 60mg /day), allergic reactions (in 0.4% of people taking 60mg /day, Meyler's 1987) and constipation (in 5% of people taking 6g /day, Meyler's 1986).

Cardiovascular disease (CVD) causes nearly half of all deaths in Europe (4 million each year) and the European Union (1.5 million each year) (BHF 2002). Worldwide, heart disease and strokes kill more than 12 million people each year and the World Health Organisation estimates that a quarter of CVD is caused by raised serum cholesterol levels (WHO 2002). The cost to people and to health services is enormous.

The use of spreads containing phytosterols or phytosterols, as part of the diet modified to control blood cholesterol concentration, could help to reduce the incidence of CVD, improve the health of people with CVD and potentially have an enormous impact on these costs. Unfortunately, although these products are available, in shops and supermarkets, and, in the UK, claims are made that they are “Clinically proven to dramatically reduce cholesterol and help to maintain a healthy heart”, they are generally more expensive than their “non-plant stanol/sterol” containing competitors.

A non-systematic review of the effects on health and serum cholesterol of dietary spreads containing phytosterols or phytosterols suggested a 25% reduction in the risk of heart disease following the use of 2g of phytosterols or phytosterols daily (Law 2000). A more recent non-systematic review supports this and claims that patients already on a blood cholesterol-reducing regimen e.g. taking statins, can benefit by further reduction in blood

cholesterol level as a result of eating foods supplemented with phytosterols or phytosterols (Katan 2003). An independent and systematic review is needed, that will enable individuals to balance any benefits and harms with the extra costs of these products. This review will evaluate trials where subjects have used dietary spreads (or other food products) supplemented with phytosterol esters, phytostanol esters, free phytosterols or free phytosterols. Our focus will be on spreads because sterols, stanols and their esters are more soluble in fat than in water and because they are likely to be used regularly by a higher proportion of the population than some of the other supplemented foods. Also spreads are probably more suitable for use in clinical trials, because it is easier to achieve the desired concentration and uniformity of distribution of sterols in a fat based spread than in e.g. fat free yoghurt. However, we will not exclude any trial simply on the basis of the food used as a vehicle for the intervention (phytosterol or phytostanol). The effects of these products on blood cholesterol levels and cardiovascular events of normal healthy individuals, those thought to have age or diet related hypercholesterolaemia and those who have some form of inherent hypercholesterolaemia will be included in the review.

OBJECTIVES

1. To determine the effects of phytosterols, phytosterols or their esters, ingested in supplemented foods, on blood cholesterol concentrations and cardiovascular disease;
2. To look for adverse effects e.g. on nutritional status or physiological function;
3. To study/comment on, possible effects of cost.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised control trials of parallel or crossover design will be studied. We will include all studies with primary or secondary outcomes, with or without cardiovascular outcomes. Only parallel studies will contribute information on deaths and cardiovascular events. We make no assumptions about blinding, but adequacy of blinding will be considered in deciding the quality of each study. Inclusion of a study in this review will be dependent on quality.

Types of participants—Adults and/or children at any risk of cardiovascular disease and with normal or raised blood cholesterol levels (>5.2 mmol/L). All settings will be included e.g. ward, outpatient clinic, community. Studies will be stratified by age, risk, disease status or setting.

Types of interventions—Phytosterols and/or phytosterols or their esters incorporated into foods, at any dose, and which might form part of a normal diet. These products need to be eaten at least daily and for at least four weeks. This is a minimum duration. Longer studies/follow up will be required to observe any effects on cardiovascular outcomes. The products studied will be the phytosterols or phytosterols formulated in a suitable vehicle e.g. margarine spread, yoghurt, cheese spread, cereal bar etc. The effects of these products in a

treatment group will be compared to the effects a placebo (vehicle only) in a control group. Only properly controlled trials, as defined above, will be included. Data on compliance will be collected and tabulated on the data collection form.

Types of outcome measures

Primary outcomes: Efficacy: Serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) and cardiovascular events.

Secondary outcomes:

- Efficacy: Mortality, quality of life, weight, blood pressure, blood glucose concentration.
- Safety: Evidence for reduced absorption of fat soluble vitamins (A, D and E) and other effects on nutritional status e.g. on glycoproteins, on bowel function. Any reported side effects including anorexia, cramping, diarrhoea, constipation and allergic reactions. If individual patient data are available, we will look for instances where blood cholesterol levels appeared to be unchanged or increased by the treatment.
- Economic: Costs.

Search methods for identification of studies

Electronic searches—Searching will be carried out on *The Cochrane Library*, MEDLINE, EMBASE, the Meta-register of Controlled Trials (www.controlled-trials.com), LILACS and SIGLE. The following search strategy (for MEDLINE on Ovid) will be adapted for each of these databases. In addition a standard filter for finding RCTs will be used for MEDLINE (Dickersin 1994) and EMBASE (Lefebvre 1996)

1. exp Phytosterols/
2. exp Margarine/
3. (stanol adj3 ester\$).tw.
4. (sterol adj3 ester\$).tw.
5. (plant\$ adj5 (stanol\$ or sterol\$)).tw.
6. (staest or steest).tw.
7. phytosterol\$.tw.
8. phyto-sterol\$.tw.
9. (phytosterol\$ or phyto-sterol\$).tw.
10. (phytostanol\$ or phyto-stanol\$).tw.
11. sitosterol\$.tw.
12. (beta-sitosterol\$ or betasitosterol\$).tw.
13. sitostanol.tw.

14. (beta-sitostanol\$ or betasitostanol\$).tw.
15. campesterol\$.tw.
16. campestanol\$.tw.
17. (stigma-sterol\$ or stigmasterol\$).tw.
18. tall oil.tw.
19. todpm.tw.
20. pro-active.tw.
21. benecol.tw.
22. ((plant\$ or veget\$ or wood\$ or seed\$ or sunflower\$) adj5 (stanol\$ or sterol\$)).tw.
23. margarine.tw.
24. (phytostanyl\$ or phytosteryl\$).tw.
25. ((stanyl or steryl) adj3 ester\$).tw.
26. or/1-25
27. exp Hyperlipidemia/
28. exp Cardiovascular Diseases/
29. (coronary or cardiac or cardiovascular).tw.
30. (heart adj5 disease\$).tw.
31. (cholesterol\$ or hypercholesterol\$).tw.
32. hyperlipid\$.tw.
33. atherosclero\$.tw.
34. arteriosclero\$.tw.
35. myocard\$.tw.
36. (plasma adj3 lipid\$).tw.
37. (lipid\$ adj3 (reduc\$ or low\$)).tw.
38. or/27-37 39 26 and 38

The Cochrane Heart Group will also be asked to search their trials register. The search will not be limited to English, and all non-English papers that appear relevant will be translated if possible.

Searching other resources—The reference lists of comprehensive reviews of stanol and sterol esters and all included studies will be checked, and attempts will be made to contact manufacturers, and the authors of all included studies, to identify missed or unpublished trials.

Data collection and analysis

Data collection—Two reviewers will independently assess inclusion of studies using an in/out form. Differences between reviewers' results will be resolved by discussion and, when necessary, in consultation with a third reviewer.

A data abstraction form will be specifically designed for this review. Data on type of study, participants, interventions, and outcomes, as described above in the selection criteria section, will be abstracted. For trials of crossover design, within patient differences between trial periods will be data extracted (with standard deviations), but where these data are not available change (preferably) or end data for each period will be extracted with paired t-test data (Elbourne 2002). For trials of parallel design change data for each arm (with standard deviations) will be extracted preferentially, final data as a second choice. Data will be collected on males and females together, males individually and females individually. Outcome data for health events will be extracted at the latest point in parallel trials (and not used from crossover trials). For risk factor outcomes data will be extracted from the latest point available from 4 to 51 weeks, and also the latest point available from 52 or more weeks, in parallel and crossover trials.

Trial quality will be assessed according to the Cochrane Reviewers' Handbook (Clarke 2000). Quality characteristics to be examined will be:

- (1) Selection bias - recruitment method, randomisation method, allocation concealment;
- (2) Performance bias - blinding to intervention group, researchers, patients;
- (3) Attrition bias - loss to follow up;
- (4) Detection bias - blinding of researchers to assess outcomes of the intervention allocation, outcome measurement;
- (5) Compliance - adequacy of monitoring.

These will be rated on a four-point scale of systematic bias - adequate (A), unclear (B), inadequate (C) or not used (D). When possible, the reviewers will obtain further information from the authors of a report when it is unclear whether a criterion was met. The two reviewers abstracting data from reports will also assess quality and summarise each using a three-point scale of risk of bias - low, moderate or high.

In addition, data will be collected on potential effect modifiers including participants sex, baseline risk of cardiovascular disease, trial duration, stanol or sterol ester, baseline total and LDL cholesterol levels and use of lipid-lowering medication; also carbohydrate level, calorific level and vitamin status. Baseline risk of cardiovascular disease will be defined as follows: high risk are participants with existing vascular disease including a history of myocardial infarction, stroke, peripheral vascular disease, angina, heart failure or previous coronary artery bypass grafting or angioplasty; moderate risk are participants with a familial risk, dyslipidaemia, diabetes mellitus, hypertension, chronic renal failure; low risk are other participants.

Data synthesis—Primary measures of interest will be the effect of dietary supplementation on serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) cardiovascular morbidity and interventions (including non-fatal myocardial infarction, total MI, stroke, angina, heart failure, peripheral vascular disease, angioplasty and coronary artery bypass grafting)

Where appropriate, treatment/control differences in the outcomes will be combined across studies using mean differences and odds ratios in random effects meta-analyses. If trials randomised by cluster are identified the patient numbers will be reduced to an “effective sample size” as described by Hauck (Hauck 1991).

Sensitivity analysis will be used to assess robustness of results to trial duration and fixed or random effects models. Funnel plots and a simple graphical test will be used to assess for evidence of bias.

Sub-grouping and meta-regression will be used to explore the effects of the effect modifiers on the primary outcomes, and of use of crossover or parallel studies

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SOURCES OF SUPPORT

Internal sources

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- Department of Social Medicine, University of Bristol, UK.
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External sources

- Cochrane Heart Group, UK.

HISTORY

Protocol first published: Issue 2, 2004

Date	Event	Description
1 April 2008	Amended	Converted to new review format.

WHAT'S NEW

Date	Event	Description
1 April 2008	New citation required and minor changes	Change in authorship

Additional references

BHF 2002 . British Heart Foundation. Health Promotion Research Group. Department of Public Health. University of Oxford. [accessed 6 February 2003] British Heart Foundation Statistics

- Database: Annual compendium. 2002. <http://www.dphpc.ox.ac.uk/bhfhprg/stats/2000/index.html>
- Clarke 2000 . Clarke, M.; Oxman, AD. Review Manager (RevMan) [Computer program] 4.1. The Cochrane Collaboration; Oxford England: 2000. Cochrane Reviewer's Handbook. Updated June 2000
- Dickersin 1994 . Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ*. 1994; 309:1286–91. [PubMed: 7718048]
- Elbourne 2002 . Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving crossover trials: methodological issues. *International Journal of Epidemiology*. 2000; 31:140–9. [PubMed: 11914310]
- Hauck 1991 . Hauck WW, Gilliss CL, Donner A, Gortner S. Randomization by cluster. *Nursing Research*. 1991; 40(6):356–8. [PubMed: 1956815]
- Heinemann 1993 . Heinemann T, Axtmann G, Von Bergmann K. Comparison of intestinal absorption of cholesterol with different plant sterols in man. *European Journal of Clinical Investigation*. 1993; 23(12):827–31. [PubMed: 8143759]
- Hendriks 1999 . Hendriks HFJ, Weststrate JA, Van Vliet T, Meijer GW. Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects. *European Journal of Clinical Nutrition*. 1999; 53:319–27. [PubMed: 10334658]
- IFST 2000 . Institute of Food Science & Technology (UK) (IFST). [accessed 3rd March 2003] Phytosterol esters (plant sterol and stanol esters). 2000. <http://ifst.org/hotspot29.htm>
- Katan 2003 . Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R, for the Stresa Workshop Participants. Efficacy and Safety of Plant Stanols and Sterols in the Management of Blood Cholesterol Levels. *Mayo Clinic Proceedings*. 2003; 78:965–78. [PubMed: 12911045]
- Law 2000 . Law M. Plant sterol and stanol margarines and health. *BMJ*. 2000; 320:861–4. [PubMed: 10731187]
- Lefebvre 1996 . Lefebvre, C.; McDonald, S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Paper presented at the Fourth International Cochrane Colloquium; Adelaide, Australia. 20-24 Oct 1996; 1996.
- Mayes 2000 . Mayes, PA. Cholesterol Synthesis, Transport and Excretion. In: Murray, RK.; Granner, DK.; Mayes, PA.; Radwell, VW., editors. *Harper's Biochemistry*. Vol. 25. McGraw-Hill; London: 2000. p. 285
- Meyler's 1986 . Dukes, MNG., editor. *Side Effects of Drugs Annual 10: A worldwide yearly survey of new data and trials*. Elsevier; Amsterdam: 1986. p. 389
- Meyler's 1987 . Dukes, MNG., editor. *Side Effects of Drugs Annual 11: A worldwide yearly survey of new data and trials*. Elsevier; Amsterdam: 1987. p. 383
- Meyler's 1988 . Dukes, MNG., editor. *Meyler's Side Effects of Drugs: An encyclopedia of adverse reactions and interactions*. 11th Edition. Elsevier; Amsterdam: 1988.
- Moreau 2002 . Moreau RA, Whitaker BD, Hicks KB. Phytosterols, phytostanols and their conjugates in foods: structural diversity, quantitative analysis, and health-promoting uses. *Progress in Lipid Research*. 2002; 41(6):457–500. [PubMed: 12169300]
- Pollak 1953 . Pollak OJ. Reduction of blood cholesterol in man. *Circulation*. 1953; 7:702–6. [PubMed: 13042924]
- Pollak 1981 . Pollak, OJ.; Kritchevsky, D. *Monographs on atherosclerosis*. Clarkson, TB.; Kritchevsky, D.; Pollak, OJ., editors. Vol. 10. Karger S; New York: 1981. p. 139-57.
- Weststrate 1998 . Weststrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *European Journal of Clinical Nutrition*. 1998; 52(5):334–43. [PubMed: 9630383]
- WHO 2002 . World Health Organization (WHO). [accessed 16th Feb 2003] Cardiovascular Death and Disability can be reduced more than 50 percent. 2002. <http://www.who.int/mediacentre/releases/pr83/en/>

* Indicates the major publication for the study