# Screening for hypercholesterolaemia in primary care: randomised controlled trial of postal questionnaire appraising risk of coronary heart disease

Brian Hutchison, Stephen Birch, C Edward Evans, Laurie J Goldsmith, Barbara A Markham, John Frank, Michael Paterson

Department of Family Medicine, Centre for Health Economics and Policy Analysis, Department of Clinical Epidemiology and Biostatistics, McMaster University, Health Sciences Centre Room 3H1E, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5

Brian Hutchison, *associate professor*

Centre for Health Economics and Policy Analysis, Department of Clinical Epidemiology and Biostatistics, McMaster University

Stephen Birch, *professor*

Department of Family Medicine, McMaster University

C Edward Evans, *professor*

Department of Clinical Epidemiology and Biostatistics, McMaster University

Laurie J Goldsmith, *research coordinator*

Centre for Health Economics and Policy Analysis, McMaster University

Barbara A Markham, *research coordinator*

continued over

*BMJ* 1998;316:1208–13

## Abstract

**Objectives:** To validate a self administered postal questionnaire appraising risk of coronary heart disease. To determine whether use of this questionnaire increased the percentage of people at high risk of coronary heart disease and decreased the percentage of people at low risk who had their cholesterol concentration measured.

**Design:** Validation was by review of medical records and clinical assessment. The questionnaire appraising risk of coronary heart disease encouraged those meeting criteria for cholesterol measurement to have a cholesterol test and was tested in a randomised controlled trial. The intervention group was sent the risk appraisal questionnaire with a health questionnaire that determined risk of coronary heart disease without identifying the risk factors as related to coronary heart disease; the control group was sent the health questionnaire alone.

**Setting:** One capitation funded primary care practice in Canada with an enrolled patient population of about 12 000.

**Subjects:** Random sample of 100 participants in the intervention and control groups were included in the validation exercise. 5686 contactable patients aged 20 to 69 years who on the basis of practice records had not had a cholesterol test performed during the preceding 5 years were included in the randomised controlled trial. 2837 were in the intervention group and 2849 were in the control group.

**Main outcome measures:** Sensitivity and specificity of assessment of risk of coronary heart disease with risk appraisal questionnaire. Rate of cholesterol testing during three months of follow up.

**Results:** Sensitivity of questionnaire appraising coronary risk was 87.5% (95% confidence interval 73.2% to 95.8%) and specificity 91.7% (81.6% to 97.2%). Of the patients without pre-existing coronary heart disease who met predefined screening criteria based on risk, 45 out of 421 in the intervention group (10.7%) and 9 out of 504 in the control group (1.8%) had a cholesterol test performed during follow up ($P<0.0001$). Of the patients without a history of coronary heart disease who did not meet criteria for cholesterol testing, 30 out of 1128 in the intervention group (2.7%) and 18 out of 1099 in the control group (1.6%) had a cholesterol test ($P=0.175$). Of the patients with pre-existing coronary heart disease, 1 out of 15 in the intervention group (6.7%) and 1 out of 23 in the control group (4.3%) were tested during follow up ($P=0.851$, one tailed Fisher's exact test).

**Conclusions:** Although the questionnaire appraising coronary risk increased the percentage of people at high risk who obtained cholesterol testing, the effect was small. Most patients at risk who received the questionnaire did not respond by having a test.

## Introduction

Opportunistic approaches to screening for hypercholesterolaemia are widely advocated.[1–8] However, studies of this approach for hypercholesterolaemia,[9–11] cervical carcinoma,[10–18] breast cancer,[10–13 15–23] and hypertension[14 15 21] have repeatedly shown that a substantial percentage of eligible patients, often most, are not screened, even when interventions designed to improve coverage are used.[10 11 14–20 22] In only a few instances have rates of coverage been reported that might be considered satisfactory—for Papanicolaou smear testing,[21–23] clinical breast examination,[21] and blood pressure measurement.[10] In our study of selective opportunistic screening for hypercholesterolaemia in a Canadian primary care group practice, 38% of patients who met the practice's criteria for screening were tested over 45 months.[24]

Among the factors that limit the effectiveness of opportunistic screening are non-attendance at the practice by healthy patients and the tendency for those who seek care to have immediate health problems that take precedence over preventive issues. These limitations might be overcome by active screening approaches that seek to recruit people who meet predetermined criteria for testing. To assess this strategy, we developed and evaluated an active screening intervention for hypercholesterolaemia using a postal self administered questionnaire appraising the risk of coronary heart disease.

**Toronto Working Group's criteria for cholesterol measurement**[5 6]

For men aged 35-39, one or more, and for women aged 20-69 years and men aged 20-34 and 60-69, two or more of:
- Hypertension (controlled or uncontrolled)
- Diabetes mellitus
- Smoking, especially when this is resistant to efforts to stop
- Severe or abdominal obesity
- Family history of hypercholesterolaemia or coronary heart disease, particularly myocardial infarction or death from coronary heart disease in a parent or sibling before the age of 60

## Subjects and methods

The objectives of this research were (*a*) to validate assessment of the risk of coronary heart disease by self administered questionnaire and (*b*) to determine whether posting a questionnaire appraising the risk of coronary heart disease to patients in primary care increases the percentage of people at high risk of coronary heart disease who have serum cholesterol concentration measured and decreases the percentage of people at low risk who are tested.

The setting was a capitation funded primary care practice with an enrolled patient population of about 12 000, of whom 7785 were between the ages of 20 and 69 years. For the 45 months before the beginning of the research the practice had been performing protocol based selective opportunistic screening for hypercholesterolaemia among its adult patients. The research protocol received ethics approval from the Ethics Review Committee of the McMaster University Faculty of Health Sciences.

### Validation of risk appraisal questionnaire

For a random subset of 100 subjects drawn from both intervention and control groups, risk of coronary heart disease on the basis of responses in the health questionnaire was validated by a face to face clinical assessment with a research nurse. Criteria for assigning risk were those of the Toronto Working Group on Cholesterol Policy (box).[5 6] Three months after completing the questionnaire subjects were assessed in their homes by a nurse after she had reviewed their clinical records. The review of clinical records was intended to identify any history of myocardial infarction or angina, use of glyceryl trinitrate or other nitrates, smoking, hypertension, diabetes mellitus, and family history of hypercholesterolaemia or coronary heart disease. The nurse's clinical assessment included taking a history to identify coronary heart disease and risk factors for the disease, and any changes in these two since completion of the questionnaire; examination of current drug treatment; and measurement of height and weight. Blood pressure was not measured because increased blood pressure on a single occasion is insufficient to diagnose hypertension.

### Randomised study of risk appraisal questionnaire

Figure 1 shows the overall design of the trial. All patients of the practice between the ages of 20 and 69 years who, according to the practice's computerised cholesterol programme database, had not already been tested were randomly allocated to receive either (*a*) a health questionnaire that determined whether they were at risk of coronary heart disease without identifying the risk factors as related to coronary heart disease (control group) or (*b*) the health questionnaire and a questionnaire appraising risk of coronary heart disease that encouraged those meeting criteria for cholesterol measurement to have a cholesterol test (intervention group).

The questionnaire appraising risk of coronary heart disease (fig 2) made operational the criteria for cholesterol measurement developed by the Toronto Working Group on Cholesterol Policy (box).[5 6] To minimise labelling and arousing fear, people who met these criteria for cholesterol testing were not advised of their high risk of coronary heart disease but were encouraged to have a cholesterol test performed if they had not been tested in the previous five years. Although the Toronto Working Group is silent on the subject, the Canadian Task Force on the Periodic Health Examination recommends five years between cholesterol tests for people with initially normal results.[1] Those not meeting the screening criteria of the Toronto Working Group were advised that they did not need cholesterol testing. A requisition for cholesterol testing that included the hours when the practice took blood samples was included in the intervention group's package. Covering letters were signed by the principal investigator and the practice doctors. The covering letters included a statement that a decision not to participate in the project would in no way jeopardise the patient's care.

Institute for Clinical Evaluative Sciences, Sunnybrook Health Science Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5

John Frank, *professor*

Michael Paterson, *research coordinator*

Correspondence to: Dr Hutchison hutchb@fhs.mcmaster.ca

C Edward Evans has since died

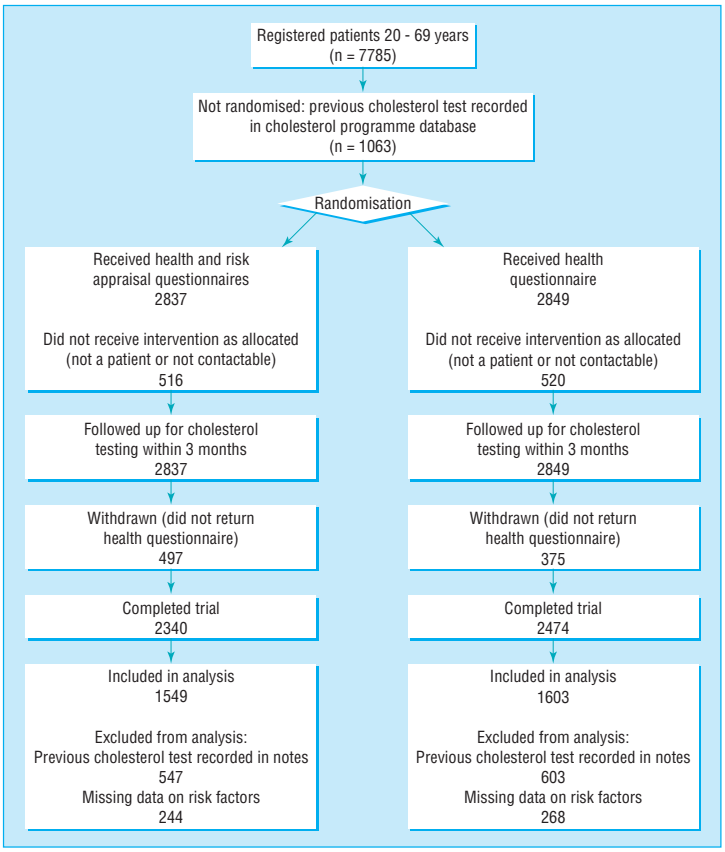



**Fig 1** Design of study

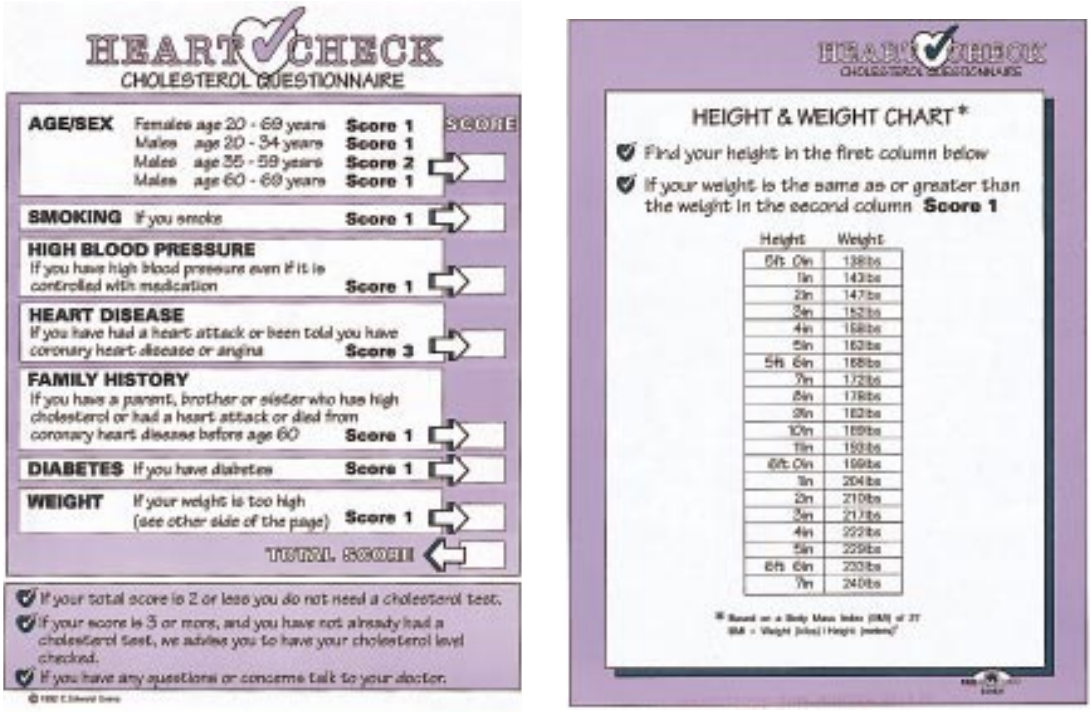



**Fig 2** Questionnaire appraising risk of coronary heart disease

Questionnaires were posted in 26 waves two weeks apart. This ensured that the work of drawing blood samples for cholesterol testing, processing test results, handling inquiries related to cholesterol, following up abnormal test results, and managing newly identified cases of hypercholesterolaemia would be spread over time so as not to overwhelm the practice resources. Patients in the intervention and control groups were followed up for three months after the questionnaire was initially sent to determine whether they had had a cholesterol test.

To minimise contamination, patients were allocated by household unit, rather than individually. A second and third copy of the questionnaire were sent to non-respondents, and any remaining non-respondents were surveyed by telephone. We conducted intensive follow up to obtain as complete information as possible about subjects' risk of coronary heart disease.

For half of the 26 waves, follow up was immediate. In the other half, follow up was delayed until the end of the three months' follow up for cholesterol testing to reflect how the risk appraisal questionnaire might ultimately be used in clinical practice—that is, with a single posting. Study results were analysed separately for the two follow up conditions to determine whether the follow up procedure influenced the likelihood of subjects in the intervention group having their serum cholesterol tested.

We estimated that the practice would provide a sample size of about 2400 subjects (1200 per group) who did not have pre-existing coronary heart disease and who met the Toronto Working Group's criteria for cholesterol screening. Setting $\alpha$ at 0.05 (two tailed) and $\beta$ at 0.1, we assumed an 80% return rate on the health questionnaire and a 1.3% uptake of cholesterol screening in the control group over the three months of follow up (on the basis of screening uptake during the first 33 months of the opportunistic screening programme). This gave us greater than 99% power to detect an absolute difference between screening rates of 10% in the intervention and control groups, with a 95% confidence interval on the difference of 7.8% to 12.2%. We considered 10% to be the minimum clinically important difference.

A check on the completeness of the practice's cholesterol programme database found that a substantial number of cholesterol tests were recorded in patient charts but not in the database. As a result, the charts of all patients between the ages of 20 and 69 years for whom there was no record of cholesterol testing in the programme database were reviewed by trained chart abstractors. A search was conducted for all cholesterol tests recorded in the chart. Laboratory reports, hospital discharge summaries, reports of specialist consultations, and records obtained from previous family physicians were examined. Patients without a record of cholesterol testing in the five years before the questionnaire was sent were included in the analysis. Separate analyses were conducted for those with and without pre-existing coronary heart disease.

Because patients were randomised by household unit, rather than individually, we used the analytical procedure proposed by Donner et al to correct for the effect of cluster allocation in testing the statistical significance of and computing 95% confidence intervals on differences between the intervention and control groups in the percentage of patients who received a cholesterol test during follow up.[25] We computed the required intracluster correlation ($\hat{K}$) for cholesterol testing on the basis of all patients in the practice aged 20 to 69 years for whom data were available. For all other analyses that entailed comparisons of proportions we used $\chi^2$ tests or Fisher's exact test.

**Table 1** Clinical validation of questionnaire appraising risk of coronary heart disease. Values are numbers of patients

| | Risk of heart disease by clinical assessment | | |
|---|---|---|---|
| | High | Low | Total |
| **Risk of heart disease by questionnaire** | | | |
| High | 35 | 5 | 40 |
| Low | 5 | 55 | 60 |
| Total | 40 | 60 | 100 |

Sensitivity = 87.5% (95% confidence interval 73.2% to 95.8%)
Specificity = 91.7% (81.6% to 97.2%)
Positive predictive value = 87.5% (73.2% to 95.8%)
Negative predictive value = 91.7% (81.6% to 97.2%)
Proportion inappropriately labelled = 10% (4.9% to 17.6%).

## Results

### Validation of risk appraisal questionnaire

Table 1 shows the results of the clinical validation of measuring risk of coronary heart disease by questionnaire. Of 100 subjects assessed clinically by the research nurse, five had false positive and five false negative results with the questionnaire. The sensitivity of questionnaire measurement of risk of coronary heart disease was 87.5% (95% confidence interval 73.2% to 95.8%); specificity was 91.7% (81.6% to 97.2%).

### Randomised study of risk appraisal questionnaire

Of the 7785 patients aged 20 to 69 years, 1063 had been previously tested according to the practice's computerised cholesterol programme database and were not included in the randomised study. Of the 6722 patients randomly allocated, 454 (6.8%) did not consider themselves to be part of the practice, 582 (8.7%) could not be contacted, and 872 (13.0%) did not respond. The response rate was 71.6% (4814/6722) among all randomised patients and 84.7% (4814/5686) when those who did not consider themselves part of the practice and those who could not be contacted were excluded from the denominator. Among contactable patients the response rate was 84.4% (2506/2970) for those receiving immediate follow up and 85.0% (2308/2716) for those who received delayed follow up.

The intervention and control groups were similar in age and sex distribution. The mean age of both intervention and control group subjects was 38.8 years (SD 12.5 years in both groups). Women comprised 53.6% of the intervention group and 53.7% of the control group. More subjects in the control group than in the intervention group (31.4% (504/1603) *v* 27.2% (421/1549); $\chi^2 = 6.902$, $P = 0.009$) met the Toronto Working Group's risk criteria for screening. Although patients were allocated by household, most households included only one subject. The mean number of study subjects per household (cluster size) was 1.27 in the intervention group and 1.29 in the control group. The mean correlation corrected for chance for cholesterol testing within household clusters was 0.9754. This correlation was used in the analysis of results to adjust for the effects of cluster allocation according to the method developed by Donner et al.[25]

Table 2 shows the overall results. Of those without pre-existing coronary heart disease who met the Toronto Working Group's criteria for screening, 45 out of 421 subjects in the intervention group (10.7%) and 9 out of 504 subjects in the control group (1.8%) had a cholesterol test performed during the three months after the initial questionnaire posting ($P < 0.0001$ after adjustment for cluster). In both the intervention and control groups the percentage of subjects tested was not significantly different in those receiving immediate or delayed follow up. In the intervention group 26 out of 228 (11.4%) who received immediate follow up and 19 out of 193 (9.8%) who received delayed follow up had a cholesterol test ($\chi^2 = 0.266$, $P = 0.606$). In the control group 4 out of 275 (1.45%) who had immediate follow up and 5 out of 229 (2.18%) who had delayed follow up were tested ($\chi^2 = 0.378$, $P = 0.538$). Of the patients without a history of coronary heart disease who did not meet the criteria of the Toronto Working Group for cholesterol testing, 30 out of 1128 subjects in the intervention group (2.7%) and 18 out of 1099 subjects in the control group (1.6%) had a cholesterol test during the three month follow up period ($P = 0.175$ after adjustment for cluster). Of the 38 subjects with pre-existing coronary heart disease, 1 out of 15 subjects in the intervention group (6.7%) and 1 out of 23 in the control group (4.3%) had a cholesterol test during the three months of follow up ($P = 0.851$ in one tailed Fisher's exact test).

## Discussion

The questionnaire appraising risk of coronary heart disease increased the percentage of people at high risk of disease who obtained cholesterol testing, but the effect was modest (and slightly less than the minimum clinically important difference we set before the study). Most of the patients at risk who received the risk appraisal questionnaire did not respond to its encouragement to obtain testing. Moreover, use of the questionnaire did not reduce the rate of cholesterol testing among people at low risk, even though it provided reassurance that cholesterol testing was unnecessary. Because few patients at low risk were tested during the three month follow up, our study had limited power to detect differences between intervention and control subjects in the proportion of low risk patients tested. Our results show, however, that the absolute impact on inappropriate testing in either direction is likely to be small.

The limited impact of the risk appraisal questionnaire may be partly because the practice had been conducting selective opportunistic screening for hypercholesterolaemia during the 45 months before the beginning of this trial. During that time 38% of patients

**Table 2** Proportions (percentages) of subjects who had a cholesterol test within three months of intervention according to risk of coronary heart disease

| | Toronto Working Group's risk criteria for screening | |
|---|---|---|
| | Met | Not met |
| **Risk appraisal questionnaire** | | |
| Intervention group | 45/421 (10.7)* | 30/1128 (2.7)† |
| Control group | 9/504 (1.8) | 18/1099 (1.6) |
| Total | 54/925 (5.8) | 48/2227 (2.2) |
| Difference in percentages (95% CI) | 8.9 (5.7 to 12.1) | 0.18 (–1.3 to 2.8) |

*P<0.001, †P=0.1745 for intervention *v* control group after adjustment for the correlation for cholesterol testing within households.

who met the practice's criteria for screening and 42% of those who met the criteria of the Toronto Working Group were tested.[24] The 60% of patients at high risk who had not been tested opportunistically would include those who were missed because they attended the practice infrequently and those who had been offered but refused opportunistic screening. During 1994, 75% of patients aged 20 to 69 (84% of women and 59% of men) were seen at least once. Because patients were exposed to the opportunistic screening programme for a mean of 39.1 months, comparatively few patients would not have been seen at all during the period of systematic opportunistic screening. In semistructured interviews conducted at the end of the evaluation of the opportunistic screening programme the doctors and nurses of the practice indicated that if patients at risk were not tested it was mainly because doctors and patients tended to give priority to immediate healthcare problems. All but one of them believed that patients' refusal of or non-compliance with testing would account for only a small proportion of failures to test people at increased risk of coronary heart disease.

**Key messages**

- Of patients at high risk of coronary heart disease, 10.7% who received a risk appraisal questionnaire with a general health questionnaire and 1.8% of those who received the general health questionnaire alone had a cholesterol test within the following three months
- Of patients at low risk, 2.7% of patients receiving the risk appraisal questionnaire and 1.6% of control subjects had a cholesterol test
- Most patients at risk who received the risk appraisal questionnaire did not seek a test
- Further research is needed to identify factors contributing to low uptake of cholesterol testing among people at high risk of coronary heart disease even when encouragement is given

### Alternative screening strategy

An alternative active screening strategy would be to include cholesterol screening in a scheduled periodic health examination offered systematically to all middle aged patients. This strategy was used in the Oxcheck trial[26] and in a Welsh general practice study.[27] In the Oxcheck trial around 66% of registered patients aged 35 to 64 years attended for a health check after a two stage process which entailed a postal questionnaire and an invitation for respondents to receive a health check from a trained nurse. The health check included non-selective screening for hypercholesterolaemia.[26] In a Welsh general practice serving 10 000 patients 62% of invited patients aged 25 to 55 years attended a nurse run lifestyle intervention clinic for the identification and treatment of risk factors for coronary heart disease.[27] Implementation of screening strategies of this type, whether cholesterol testing was selective or non-selective, would require a substantial commitment of resources.

### Further research

Further research to identify factors contributing to low uptake of cholesterol testing among people at high risk of coronary heart disease—even with encouragement to obtain testing—is clearly desirable. The failure of our questionnaire to have an important effect on cholesterol testing could be related to its low key content and advice giving (rather than information giving) nature. Although the questionnaire assessed risk, it did not explicitly say that a high score meant an increased risk of coronary heart disease. The questionnaire and covering letter provided no information about coronary heart disease or its risk factors but advised those with high scores to obtain cholesterol testing and reassured those with low scores that cholesterol testing was not required. Perhaps an instrument that was more explicit about the risk of coronary heart disease and the potential benefits of lowering cholesterol concentration might have had more impact. Patients' perceptions about the risk of coronary heart disease and about lowering cholesterol concentration may underlie non-response to this intervention, which means that patients may be resistant to information as well as to advice.

This work is dedicated to the memory of C Edward (Ted) Evans, who contributed enormously to this project and whose death was a great loss to all of us who were privileged to work with him.

Contributors: BH initiated the study with SB, assembled the research team, participated in the conceptualisation of the project, drafted the methods section of the research protocol, supervised research staff in the collection and analysis of data, and drafted the paper. He is guarantor of the study. SB and BAM participated in all phases of the research from conceptualisation to writing of the paper. CEE (deceased) participated in the development of the protocol, designed the coronary heart disease risk appraisal questionnaire, and participated in the implementation of the study. LJG played a major role in data collection and analysis and participated in the writing of the paper. JF participated in the conceptualisation of the project, and the development of the research protocol, and the writing of the paper. MP participated in the data analysis and writing of the paper.

Funding: BH and SB are supported as national health research scholars by Health Canada. This study was supported by a research grant from the Ontario Ministry of Health.

Conflict of interest: None.

1 Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1993 update. 2. Lowering the blood total cholesterol level to prevent coronary heart disease. *Can Med Assoc J* 1993;148:521-38.
2 European Atherosclerosis Society Study Group. Strategies for the prevention of coronary heart disease. *Eur Heart J* 1987;8:77-88.
3 International Task Force for the Prevention of Coronary Heart Disease. Prevention of coronary heart disease: scientific background and new clinical guidelines. Recommendations of the European Atherosclerosis Society. *Nutr Metab Cardiovasc Dis* 1992;2:113-56.
4 Canadian Consensus Conference on Cholesterol. Final report. *Can Med Assoc J* 1988;139(suppl):1-8.
5 Toronto Working Group on Cholesterol Policy. *Detection and management of asymptomatic hypercholesterolaemia: a policy document.* Toronto: Ontario Ministry of Health, 1989.
6 Toronto Working Group on Cholesterol Policy. Asymptomatic hypercholesterolaemia: a clinical policy review. *J Clin Epidemiol* 1990;43: 1029-121.
7 Royal College of General Practitioners. *Guidelines for the management of hyperlipidaemia in general practice. Towards the primary prevention of coronary heart disease.* London: RCGP, 1992. (Occasional paper 55.)
8 American College of Physicians. Clinical guidelines, part 1. Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. *Ann Intern Med* 1996;124:515-7.
9 Ohved I, Odeberg H, Rastam L. Opportunistic screening for hypercholesterolaemia with participants selected by the general practitioner: inclusion and drop-out rate. *Fam Pract* 1991;8:360-6.

10 Cheney C, Ramsdell JW. Effect of medical records' checklists on implementation of periodic health measures. *Am J Med* 1987;83:129-36.
11 Ornstein SM, Garr DR, Jenkins RG, Rust PF, Arnon A. Computer-generated physician and patient reminders: tools to improve population adherence to selected preventive services. *J Fam Pract* 1991;32:82-90.
12 Lurie N, Manning WG, Peterson C, Goldberg GA, Phelps CA, Lillard L. Preventive care: do we practice what we preach? *Am J Public Health* 1987;77:801-4.
13 McPhee SJ, Richard RJ, Solkowitz SN. Performance of cancer screening in a university general internal medicine practice: comparison with American Cancer Society guidelines. *J Gen Intern Med* 1986;1:275-81.
14 Rosser WW, McDowell I, Newell C. Use of reminders for preventive procedures in family medicine. *Can Med Assoc J* 1991;145:807-14.
15 Shank JC, Powell T, Llewelyn J. A five-year demonstration project associated with improvement in physician health maintenance behaviour. *Fam Med* 1989;21:273-8.
16 McDonald CJ, Hui SL, Smith DM, Tierney WM, Cohen SJ, Weinberger M, et al. Reminders to physicians from an introspective computer medical record: a two-year randomized trial. *Ann Intern Med* 1984;100:130-8.
17 Tierney WM, Hui SL, McDonald CJ. Delayed feedback of physician performance versus immediate reminders to perform preventive care: effects on physician compliance. *Med Care* 1986;24:659-66.
18 Schreiner DT, Petrusa ER, Rettie CS, Kluge RM. Improving physician compliance with preventive medicine procedures in a house staff training program. *Southern Med J* 1988;81:1553-7.
19 Korn JE, Schlossberg LA, Rich EC. Improved preventive care following an intervention during an ambulatory care rotation: carryover to a second setting. *J Gen Intern Med* 1988;3:156-60.
20 Cohen DI, Littenberg B, Wetzel C, Neuhauser DvB. Improving physician compliance with preventive guidelines. *Med Care* 1982;20:1040-5.
21 Dietrich AJ, Goldberg H. Preventive content of adult primary care: do generalists and subspecialists differ? *Am J Public Health* 1984;74:223-7.
22 McPhee SJ, Bird JA, Jenkins NH, Fordham D. Promoting cancer screening: a randomized, controlled trial of three interventions. *Arch Intern Med* 1989;149:1866-72.
23 Woo B, Woo B, Cook EF, Weisberg M, Goldman L. Screening procedures in the asymptomatic adult: comparison of physicians' recommendations, patient desires, published guidelines and actual practice. *JAMA* 1985;254:1480-4.
24 Hutchison B, Birch S, Evans CE, Goldsmith L, Markham B, Frank J. *Performance appraisal of opportunistic screening for hypercholesterolaemia in primary care practice.* Hamilton, Ontario: McMaster University Centre for Health Economics and Policy Analysis, 1995. ( Working Paper Series No 95-14.)
25 Donner A, Birkett N, Buck C. Randomization by cluster: sample size requirements and analysis. *Am J Epidemiol* 1981;114:906-14.
26 Muir J, Neil A, Roe L, Rusted N, Thorogood M, Mant D. Prevalence of risk factors for heart disease in OXCHECK trial: implications for screening in primary care. *BMJ* 1991;302:1057-60.
27 Jones A, Davies DH, Dove JR, Collinson MA, Brown PMR. Identification and treatment of risk factors for coronary heart disease in general practice: a possible screening model. *BMJ* 1988;296:1711-4.


*(Accepted 27 November 1997)*

# Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects

J L Tang, J M Armitage, T Lancaster, C A Silagy, G H Fowler, H A W Neil


## Abstract

**Objectives:** To estimate the efficacy of dietary advice to lower blood total cholesterol concentration in free-living subjects and to investigate the efficacy of different dietary recommendations.
**Design:** Systematic overview of 19 randomised controlled trials including 28 comparisons.
**Subjects:** Free-living subjects.
**Interventions:** Individualised dietary advice to modify fat intake.
**Main outcome measure:** Percentage difference in blood total cholesterol concentration between the intervention and control groups.
**Results:** The percentage reduction in blood total cholesterol attributable to dietary advice after at least six months of intervention was 5.3% (95% confidence interval 4.7% to 5.9%). Including both short and long duration studies, the effect was 8.5% at 3 months and 5.5% at 12 months. Diets equivalent to the step 2 diet of the American Heart Association were of similar efficacy to diets that aimed to lower total fat intake or to raise the polyunsaturated to saturated fatty acid ratio. These diets were moderately more effective than the step 1 diet of the American Heart Association (6.1% *v* 3.0% reduction in blood total cholesterol concentration; $P<0.0001$). On the basis of reported food intake, the targets for dietary change were seldom achieved. The observed reductions in blood total cholesterol concentrations in the individual trials were consistent with those predicted from dietary intake on the basis of the Keys equation.
**Conclusions:** Individualised dietary advice for reducing cholesterol concentration is modestly effective in free-living subjects. More intensive diets achieve a greater reduction in serum cholesterol concentration. Failure to comply fully with dietary recommendations is the likely explanation for this limited efficacy.



Division of Public Health and Primary Care, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE
J L Tang, *research fellow*
T Lancaster, *senior clinical lecturer*
G H Fowler, *professor of general practice*
H A W Neil, *lecturer*
Clinical Trial Service Unit and Epidemiological Studies Unit, Harkness Building, Radcliffe Infirmary
J M Armitage, *senior research fellow*
Flinders University of South Australia School of Medicine, Adelaide, Australia
C A Silagy, *professor of general practice*
Correspondence to: Dr Armitage Jane.armitage@ctsu.ox.ac.uk


*BMJ* 1998;316:1213–20

## Introduction

Blood cholesterol concentration is an important and modifiable risk factor for coronary heart disease.[1] A sustained reduction in blood total cholesterol concentration of 1% is associated with a 2-3% reduction in incidence of coronary heart disease.[2] Even small reductions in population cholesterol concentrations could therefore be worth while.

Dietary changes can reduce blood total cholesterol concentrations. Results from metabolic ward studies have shown that feasible changes in diet can reduce blood total cholesterol concentration by 10-15%.[3] The chief determinants of blood total cholesterol concentrations are dietary intake of saturated fat, polyunsaturated fat, and cholesterol.[3–6] Cholesterol concentrations are also affected by reduced energy intakes resulting in weight loss[7] and possibly by specific dietary supplements such as fibre,[8] garlic,[9] and fish oils.[10] Diets that lower cholesterol concentrations may modify some or all of these factors.

Individualised dietary counselling, usually delivered through primary care, has been proposed as a method of achieving population goals for reducing coronary artery disease by the British government in its Health of the Nation targets.[11] But, the extent to which individualised cholesterol lowering diets are effective in free-living populations is controversial. One review claimed that the effect of the usual diet advised (step 1 of the American Heart Association dietary guidelines[12]) produced too small a reduction in blood total cholesterol concentration (less than 4%) to have

much value in clinical management and that the feasibility of implementing more intensive diets was unknown.[13] Another more selective review claimed, however, that dietary counselling could achieve reductions in blood total cholesterol concentration of 10% or more in free-living subjects and, hence, could play an important part in reducing rates of coronary heart disease.[14]

In view of the public health importance of the issue, the resource implications, and the disagreements in the literature, we reviewed systematically and quantitatively the evidence from randomised trials for the efficacy of individualised counselling for lowering cholesterol concentration.

## Methods

### Identification of trials and extraction of data

We aimed to identify all unconfounded randomised trials of dietary advice to lower cholesterol concentration in free-living subjects published before 1996. Trials were eligible for inclusion if there were at least two groups, of which one could be considered a control group; treatment assignment was by random allocation; the intervention was a global dietary modification (changes to various food components of the diet to achieve the desired targets); and lipid concentrations were measured before and after the intervention.

Trials of diets to reduce fat intake in women considered to be at risk of breast cancer were included because the diets were similar to those aimed at lowering cholesterol concentration. We excluded trials of specific supplementation diets (such as with particular oils or margarine, garlic, plant sterol, or fibre supplements, etc), multifactorial intervention trials, trials aimed primarily at lowering body weight or blood pressure, and trials whose interventions lasted less than 4 weeks. Trials based on randomisation of workplace or general practice were also excluded.

To identify these trials we searched four electronic databases (Medline, Human Nutrition, EMBASE, and Allied and Alternative Medicine). These databases included trials published after 1966. We also identified trials by hand searching the *American Journal of Clinical Nutrition*, by scrutinising the references of review articles and of each relevant randomised trial, and by consulting experts on the subject.

Two of us (JLT and JMA) independently extracted data from each identified trial on to a standard form, disagreements being resolved by another of us (TL). Reports that appeared only in non-English language journals were examined with the help of translators. Trials were categorised according to their approximate target diet into four groups.[12]

- Step 1 diet of the American Heart Association or its equivalent (<30% of total energy intake as fat, with 8-10% as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.0; cholesterol intake <300 mg/day; and energy intake to achieve desirable body weight).
- Step 2 diet of the American Heart Association or its equivalent (<30% of total energy intake as fat, with 7% or less as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.4; cholesterol intake <200 mg/day; and energy intake to achieve desirable body weight).
- Diet to increase the ratio of polyunsaturated to saturated fatty acid with little or no change in total fat content.
- Low total fat diets, without changing the proportions of the different fats consumed.

The amount of advice given to achieve dietary change was categorised as intensive (3), moderate (2), or brief (1). The criteria for this categorisation were the total number of hours of counselling, the number of adviser-subject contacts, the duration of counselling, and whether special efforts had been made to achieve change (such as home visits, spouse support, food selection skills, and providing relevant foods in local shops). In general, trials rated 3 had more than two sessions or contacts between adviser and patient per month, those rated 2 had between one and two contacts per month, and those rated 1 had on average less than one contact per month.

Compliance was estimated by comparing self reported dietary consumption during the intervention with the targets for each diet and by comparing the fall in blood total cholesterol concentration predicted by the Keys equation,[6] using information from the self reported dietary data, with the observed fall in blood total cholesterol concentration.

### Statistical analysis

For each comparison within each trial we computed the absolute difference (in mmol/l) in the mean change in blood total cholesterol values (baseline minus final value) between the intervention and control group. (No distinction was made between serum or plasma cholesterol values.) We expressed this difference as a percentage change in blood total cholesterol concentration using a mean of the baseline values as the denominator. The principal end point for each comparison was the percentage reduction in cholesterol concentration at the end of the intervention or at 12 months, whichever was the sooner (although we also considered reductions in cholesterol concentration at different time points). The standard error (SE) of the difference $(x_1-x_0)$ for each comparison within each trial was calculated using the formula $SE(x_1-x_0)=\sqrt{(SD_1 2/n_1+SD_0 2/n_0)}$, where $x_1$ and $x_0$ are the mean changes over time in the intervention and control groups respectively, $SD_1$ and $SD_0$ are the standard deviations of these mean changes, and $n_1$ and $n_0$ are the number of subjects in each group.[15] When the values for SD were not given we imputed values[16] using as much information as was available from that trial. The summary effect for each grouping of different trials was derived from the average of the means of each separate trial weighted by $1/SE^2$ for each trial.[15] For studies with more than one intervention group the standard errors were adjusted to take account of the control group having been used more than once. Results are presented as mean percentage changes in blood total cholesterol concentration with 95% confidence intervals.

Similar methods were used to assess changes in reported dietary intake. To compute each change in a dietary factor requires up to four dietary measurements, each with their own measurement error and with additional correlated changes in saturated and

polyunsaturated fatty acid intakes. The estimates of achieved dietary intake are therefore imprecise. For this reason, the confidence limits around the predicted values are likely to be much wider than those around the achieved reductions in cholesterol concentration. Some trials reported insufficient information to allow calculations of predicted cholesterol reductions based on the Keys equation.

We performed all analyses (including weighted means, tests for heterogeneity, significance tests, and between group comparisons) using regression techniques in SAS 6.07. We explored statistical heterogeneity[17] by comparing the observed results in different categories of trials grouped according to type of diet, intensity of advice, and type of patients.

## Results

### Description of trials

We identified published reports of 133 randomised trials of some type of dietary advice to lower blood cholesterol concentration in free-living subjects; we did not find any unpublished trials. Sixty five trials were excluded because the intervention entailed supplementation with a specific dietary factor such as fish oil, cooking oil, or a modified fat product, and a further 34 were excluded because dietary advice was part of a multifactorial intervention. Five trials were excluded because they did not have an appropriate untreated control group,[18–22] three trials because they reported insufficient data for analysis,[23–25] three trials because lowering body weight was their primary aim,[26–28] two trials because reducing other coronary risk factors and not cholesterol concentration was their primary aim,[29 30] and one trial because a large proportion of subjects were taking tamoxifen, which alters blood cholesterol concentration.[31] This left 19 trials,[32–52] yielding 28 comparisons eligible for inclusion in this report. Information about the trial reported by Leren is included in three publications,[44–46] and the American diet-heart study includes seven different dietary comparisons.[37]

The table summarises the 19 trials. All stated that they were randomised, although the method of randomisation was rarely reported, and efforts had been made in most to blind those assessing results. In most of these trials the numbers of patients included in the laboratory analyses were given (the percentage analysed in the table). Five trials were in patients with coronary heart disease and the aim of the study was secondary prevention of coronary heart disease, four in subjects with raised cholesterol concentration, three in patients with raised blood pressure, four (yielding nine comparisons) in healthy adult volunteers, two in women at increased risk of breast cancer, and one in children. Most trials were in parallel groups but two were crossover in design. In the main analyses the authors assumed that the people who were not included in the reported analyses of the trial would have behaved in a way similar to those in the group to which they were allocated. An alternative assumption is that these people did not achieve any dietary change or change in their blood cholesterol concentration, and we also calculated estimates under this assumption.

### Grouping of trials

The table groups trial comparisons according to their target diet. Dietary interventions that entailed both a decrease in total fat intake and an increase in the ratio of polyunsaturated to saturated fatty acid but without stated targets and those that differed from the standard diets of the American Heart Association were grouped with the diet they most closely resembled. In eight comparisons the intervention was roughly equivalent to the association's step 1 diet and in nine to the step 2 diet. In seven comparisons the intervention diet was primarily an increase in ratio of polyunsaturated to saturated fatty acid without a change in the total fat intake. The target diet in the early trial by Leren was not clearly described but we judged it to be an increase in ratio of polyunsaturated to saturated fatty acid concentration on the basis of information given on fat intake in the Norwegian population at that time.[44–46] In four trials the target diet was primarily reduced or low total fat intake. In almost all trials which provided information on the methods of dietary intervention, the methods were categorised as moderate or intensive (table), thereby not allowing any discrimination by intensity of advice.

The duration of follow up varied from six weeks to five years. The longer trials had coronary heart disease events as the primary outcome, and, in general, the shorter trials specifically measured lipid concentrations. Thirteen trials had a follow up of at least six months and provided 22 comparisons. The average baseline blood total cholesterol concentration was 6.3 mmol/l.

### Overall effect of dietary advice on blood total cholesterol

The overall weighted mean reduction in blood total cholesterol concentration across all dietary comparisons was 5.7% (95% confidence interval 5.2% to 6.3%) using either the final reduction in cholesterol concentration at the end of the intervention or at 12 months (whichever was the sooner). For the 22 comparisons available from trials of at least six months duration, the weighted mean reduction in blood cholesterol concentration was 5.3% (4.7% to 5.9%) (figure) or, if it was assumed that subjects lost to follow up experienced no change, the mean reduction in cholesterol concentration in the longer trials was 4.5% (3.9% to 5.1%). There was obvious statistical heterogeneity between the percentage reductions in blood cholesterol concentration observed in the individual comparisons of more than six months ($\chi^2_{21} = 104$, $P < 0.001$), and this was not explained by grouping the trials by category of diet (see below). Trials published before 1981 (about halfway between the first and most recently published studies) achieved greater mean reductions in blood total cholesterol concentration (7.0% ( 6.1% to 7.9%)) than those published later (3.9% (3.1% to 4.7%)) ($\chi^2_1 = 26$, $P < 0.001$). But all except one of the earlier studies were of diets that were more intensive than the step 1 diet of the American Heart Association.

### Reductions in blood cholesterol by category of diet

There were significant differences between the reductions in blood cholesterol concentration observed with the four different categories of diet

Summary information about included trials. Studies cited more than once have several dietary comparisons within the study. Numbers in parentheses permit cross referencing to figure

| Study* | Sex | Primary end point | Baseline cholesterol (mmol/l) | Percentage of energy intake as fat (saturated, poly-unsaturated) in control group | Saturated fatty acid intake achieved as % of total energy intake | P/S (control, intervention) | Change in polyunsaturated fat as % of energy intake | Predicted% reduction in cholesterol† | Intensity rating‡ | Maximim follow up (months) | No randomised (intervention/ control group) | Percentage analysed§ | Reduction in cholesterol at end or at 12 months (%) (SE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **American Heart Association step 1 diets** | | | | | | | | | | | | | |
| Demark-Wahrenfreid et al 1990[32] | M, F | Lipids | 7.2 | 37 (11, 6) | 8 | 0.5, 0.6 | 0 | 5 | 2 | 3 | 20/20 | 83 | 2.3 (4.0) |
| Bloemberg et al 1991[33] | M | Lipids | 7.0 | 38 (16, 7) | 12 | 0.4, 0.8 | 3 | 5 | 2 | 6 | 39/41 | 100 | 4.3 (2.1) |
| Sarkkinen et al 1994 (A)[34] | M, F | Lipids | 6.6 | 35 (14, 4) | 10 | 0.3, 0.8 | 4 | 6 | 2 | 6 | 41/39 | 99 | 6.3 (3.4) |
| Burr et al 1989[35] | M | CHD events | 6.5 | 36 (NR) | NR | 0.4, 0.7 | NR | NC | 1 | 24 | 1018/1015 | 84 | 3.5 (0.7) |
| Sciarrone et al 1992[36] | M, F | Lipids, blood pressure | 6.2 | 37 (18, 3) | 9 | 1.1, 1.4 | 7 | 14 | 2 | 2 | 48/47 | 96 | 12.2 (2.3) |
| American diet-heart study 1968 (2C)[37] | M | Lipids | 6.0 | 36 (12, 5) | 10 | 0.5, 0.7 | 2 | 3 | 2 | 6.5 | 120/110 | 88 | 0.2 (1.7) |
| Ehnholm et al 1982[38] | M, F | Lipids | 5.7 | 39 (20, 5) | 7 | 0.3, 1.0 | 2 | 17 | 3 | 1.5 | 36/38 | 100 | 22.6 (1.8) |
| Baron et al 1990[39] | M, F | Lipids | 4.9 | 35 (NR) | NR | NR | NR | NC | 1 | 12 | 219/218 | 76 | 0.0 (2.2) |
| **American Heart Association step 2 diets** | | | | | | | | | | | | | |
| Watts et al 1992[40] | M | MAWS | 7.1 | NR | NR | NR | NR | NC | 1 | 39 | 30/30 | 83 | 12.2 (2.6) |
| Hunninghake et al 1993[41]¶ | M, F | Lipids | 7.0 | 41 (15, 8) | 7 | 0.5, 1.05 | 0 | 8 | 2 | 2 | 111/111 | 90 | 5.0 (0.8) |
| Anderson et al 1992 (1)[42] | M, F | Lipids | 6.0 | 31 (10, 7) | 9 | 0.7, 0.9 | 1 | 2 | 2 | 12 | 59/62 | 83 | 2.8 (2.6) |
| Anderson et al 1992 (2)[42] | M, F | Lipids | 6.0 | 31 (10, 7) | 8 | 0.7, 0.9 | 0 | 2 | 2 | 12 | 59/62 | 82 | 6.1 (2.6) |
| American diet-heart study 1968 (1A)[37] | M | Lipids | 5.9 | 35 (12, 5) | 7 | 0.4, 1.4 | 5 | 8 | 2 | 12 | 385/382 | 80 | 6.3 (0.9) |
| American diet-heart study 1968 (1C)[37] | M | Lipids | 5.9 | 35 (12, 5) | 9 | 0.4, 0.8 | 2 | 4 | 2 | 12 | 54/73 | 80 | 2.2 (2.1) |
| American diet-heart study 1968 (2A)[37] | M | Lipids | 5.9 | 36 (12, 5) | 7 | 0.5, 1.6 | 6 | 9 | 2 | 6.5 | 194/110 | 91 | 10.2 (1.1) |
| American diet-heart study 1968 (2D)[37] | M | Lipids | 5.9 | 40 (16, 4) | 8 | 0.2, 1.1 | 5 | 12 | 2 | 6.5 | 36/36 | 95 | 10.5 (2.5) |
| Dietary intervention study in children 1995[43] | M, F | CHD risk | 5.2 | 33 (12, 6) | 9 | 0.5, 0.6 | 0 | 3 | 2 | 12 | 334/329 | 94 | 3.1 (0.7) |
| **Diets increasing P/S** | | | | | | | | | | | | | |
| Leren 1966, 1968, 1970[44 45 46] | M | CHD events | 7.6 | 40 (NR) | NR | NR | NR | NC | 2 | 60 | 229/229 | 66 | 14.5 (1.7) |
| Woodhill et al 1978[47] | M | CHD events | 7.2 | 38 (14, 9) | 10 | 0.8, 1.7 | 6 | 7 | 1 | 84 | 221/237 | 87 | 4.1 (1.6) |
| Sarkkinen 1994 (C)[34] | M, F | Lipids | 6.5 | 35 (14, 4) | 11 | 0.3, 0.5 | 1 | 3 | 2 | 6 | 41/39 | 99 | 5.2 (3.4) |
| Kuusi 1985[48] | M, F | Lipids | 6.2 | 23 (10, 4) | 8 | 0.4, 0.9 | 3 | 4 | 3 | 3 | 40/40 | 98 | 4.0 (3.5) |
| American diet-heart study 1968 (1B)[37] | M | Lipids | 5.9 | 36 (12, 5) | 8 | 0.5, 1.8 | 8 | 9 | 2 | 12 | 390/382 | 80 | 7.6 (1.1) |
| American diet-heart study 1968 (2B)[37] | M | Lipids | 6.1 | 35 (12, 5) | 8 | 0.4, 1.8 | 8 | 10 | 2 | 6.5 | 127/110 | 89 | 5.3 (1.7) |
| Dreon et al 1990[49]¶ | M, F | Lipids | 5.0 | 29 (8, 5) | 8 | 0.7, 1.7 | 4 | 3 | 2 | 3 | 39/39 | 90 | 0.6 (2.3) |
| **Low fat diets** | | | | | | | | | | | | | |
| Research Committee 1965[50] | M | CHD | 6.8 | 42 (NR) | NR | NR | NR | NC | 2 | 48 | 132/132 | 69 | 5.7 (2.7) |
| Sarkkinen et al 1994[34] | M, F | Lipids | 6.3 | 35 (14, 4) | 12 | 0.3, 0.3 | –1 | 2 | 2 | 6 | 40/39 | 99 | 1.4 (3.4) |
| Insull et al 1990[51] | F | Fat intake | 5.7 | 37 (13, 7) | 7 | 0.5, 0.6 | 3 | 9 | 2 | 24 | 184/119 | 89 | 5.4 (1.7) |
| Boyd et al 1988[52] | F | Fat intake | 4.8 | 36 (14, 6) | 8 | 0.5, 0.6 | –2 | 7 | 2 | 12 | 148/147 | 72 | 7.1 (1.6) |

CHD=coronary heart disease. MAWS=mean absolute width of coronary segments on angiography. P/S=polyunsaturated to saturated fatty acid ratio. NR=not reported. NC=not calculable because the necessary information was not reported.

*Diets are listed in order of decreasing baseline cholesterol concentration within each group. †Predicted on the basis of the Keys equation for change in saturated and polyunsaturated fatty acid intake. ‡Intensity rating (1=least intensive, 3=most intensive). §Overall percentage in both intervention and control groups. ¶Crossover design.

($\chi^2_3 = 17$, $P < 0.001$). The estimated reduction in blood total cholesterol concentration with American Heart Association step 1 or equivalent diets, which lasted at least six months, was 3.0% (1.8% to 4.1%). That estimate depends heavily on one large study,[35] but there was no significant heterogeneity between these different comparisons ($\chi^2_4 = 6$, $P > 0.1$). The reduction in blood total cholesterol concentration with American Heart Association step 2 or equivalent diets was 5.6% (4.7% to 6.5%), but there was significant heterogeneity between the effects of different step 2 diets ($\chi^2_7 = 45$, $P < 0.001$). Among the step 2 diets the dietary intervention study in children was the only trial in children (aged 8-10) and it achieved a smaller effect (3.1% (1.7% to 4.5%))[43] than most of the other trials in this group. There was a significant difference between the effect observed in this trial and that observed in the other comparisons of step 2 diets ($\chi^2_1 = 23$, $P < 0.001$) (7.4% (6.2% to 8.6%)). Diets that increased the ratio of polyunsaturated to saturated fat reduced blood cholesterol concentration by 7.6% (6.2% to 9.0%), but there was significant heterogeneity between their

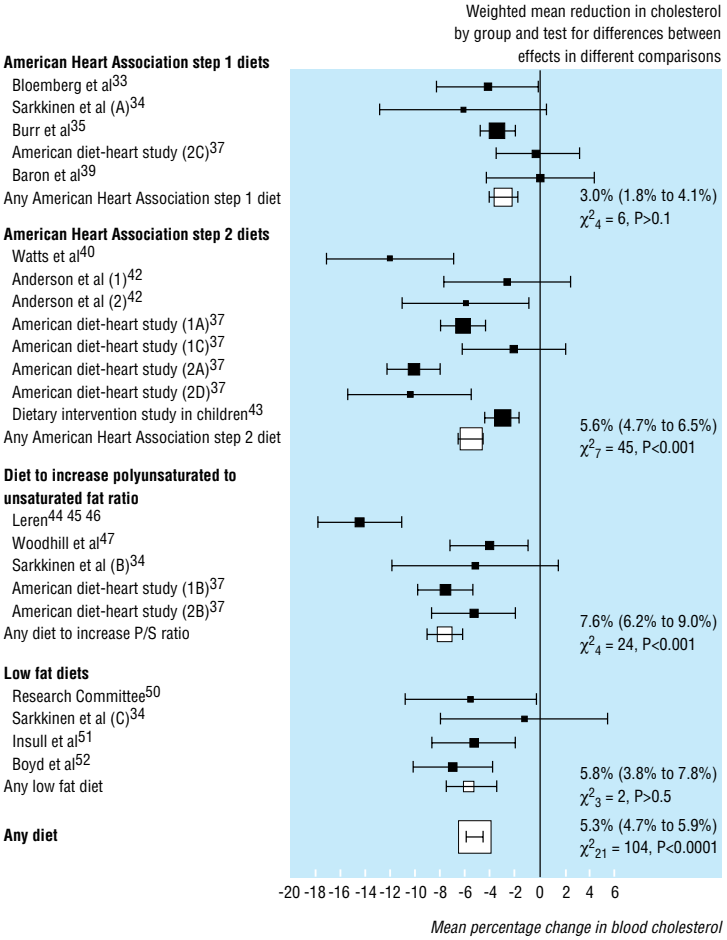
effects ($\chi^2_4 = 24$, $P < 0.001$). Among the diets that increased the ratio of polyunsaturated to saturated fatty acid concentration the estimate from the trial by Leren was extreme,[45] with significant heterogeneity between the estimated reduction in blood total cholesterol concentration in that trial (14.5% (11.2% to 17.8%)) and the other comparisons of diets increasing the ratio of polyunsaturated to saturated fat (6.2% (4.7% to 7.7%)) ($\chi^2_1 = 20$, $P < 0.001$). The four comparisons of low fat diets seemed overall to reduce blood total cholesterol concentration by 5.8% (3.8% to 7.8%) without significant heterogeneity between their separate effects.

### Reduction in cholesterol concentration by duration of intervention

Changes in blood total cholesterol concentration around 6 weeks and around 3, 6, 12, and 24 months were estimable in 11, 18, 14, 14, and 4 comparisons respectively, based on 2546, 3686, 4768, 6438, and 1688 subjects. The overall reduction in blood total cholesterol concentration attributable to dietary advice was 6.6% at about 6 weeks (including some values at 1 month and 2 months), 8.5% at about 3 months, 6.8% at 6 months, 5.5% at 12 months, and 4.4% at 24 months.

### Compliance with dietary advice

Sixteen comparisons provided some information on reported dietary intake before and during the intervention. The table shows by category of diet reported dietary consumption of type and amount of fat and the reductions in blood total cholesterol predicted by the Keys equation. Fat intakes in the control groups were variable (ranging from 29% to 42% of total energy intake) and, in general, the dietary targets were not achieved. Among the comparisons of step 1 diets only two trials[36 38] met the targets for both saturated fat and the ratio of polyunsaturated to saturated fat (10% of total fat as saturated fat and a ratio of at least 1.0); both trials also achieved the largest reductions in blood total cholesterol concentration (table). Among the comparisons of step 2 diets only the comparison of the first and second American diet heart study reached the target of 7% of energy intake as saturated fat and a ratio of polyunsaturated to saturated fatty acid concentration greater than 1.4.[37] All of the interventions to increase the ratio of polyunsaturated to saturated fat achieved an increase in the ratio but the targets varied. Similarly, all the low fat diets reduced total and saturated fat intake but the targets differed. Dietary compliance might be expected to be better in patients at higher risk of cardiovascular disease, but the reduction in blood cholesterol concentration was similar in the five comparisons among patients with coronary heart disease (5.3% (4.2% to 6.4%)) and in the 17 other comparisons of at least 6 months duration (5.3% (4.9% to 5.7%)).




Mean percentage changes (with 95% confidence intervals) in blood total cholesterol concentration for each study with at least six months of follow up according to type of diet. Studies cited more than once have several dietary comparisons within the study. Numbers in parentheses permit cross referencing to table

## Discussion

The results of metabolic ward studies of dietary lipid and cholesterol concentrations suggest that switching from the typical British diet[53] to at least the step 1 diet of the American Heart Association could reduce blood total cholesterol concentrations by an average of about 9% and that a step 2 diet might yield a further reduction of about 4%.[3] Most of the reduction in blood total cholesterol concentration is due to reductions in low density lipoprotein cholesterol concentration. Our review shows that prescribed dietary advice about as intensive as the step 1 diet would typically achieve a reduction in blood cholesterol concentration of only about 3% in free-living subjects. The more intensive diets studied typically achieved a reduction of about 6% in blood cholesterol concentration.

The most plausible explanation for the modest effects of these diets in our overview is incomplete compliance with dietary advice. In this analysis the achieved reduction in cholesterol concentration was consistent with that predicted by the Keys equation from the estimated changes in intake of saturated and polyunsaturated fatty acid. But among the comparisons of step 1 diets, only two comparisons reported reaching the target ratio of about 1.0 for polyunsaturated to saturated fat, although the target for saturated fat intake of 10% or less was reached in five of the six comparisons which provided this information. Similarly, in the step 2 diets the target ratio of polyunsaturated to saturated fat was achieved in only one out of eight comparisons and the target of 7% of energy intake as saturated fat in only three.

**Heterogeneity between study effects**

The design and results of these dietary studies differed greatly. They were conducted over 30 years and varied in their aims, in the intensity and type of intervention, and in the different baseline characteristics of the subjects included. Completeness and duration of follow up also differed. Unsurprisingly, the heterogeneity between their effects on blood cholesterol concentration was also significant.[17] Among the longer trials some, but not all, of the heterogeneity between the effects on blood cholesterol concentration seemed to be due to the type of diet recommended. Deciding which trials should be included in which groups is open to different interpretation and, although we tried to be consistent, for some trials the target diets either were not clearly stated or did not fit neatly into recognised categories such as the step 1 and 2 diets. It is important to be cautious in interpreting meta-analysis when there is evidence of significant heterogeneity, although there was no evidence that the overall results were influenced by trials with outlying values.

We used percentage rather than absolute changes in blood total cholesterol concentration because of the substantial differences in baseline diets and cholesterol values between these studies. This may reflect the period of several decades and the diverse populations in which the studies were carried out. In trials published before 1981, the mean reductions in blood total cholesterol concentration were greater than in later trials (7.0% *v* 4.0%), which may partly reflect the early predominance of more intensive diets. But we found no significant difference between the percentage reduction in blood total cholesterol concentration observed in trials with above or below average mean baseline cholesterol values (5.2% *v* 5.4% respectively).

**Methodological issues**

We included only comparisons in which the dietary advice was a single intervention. Excluding trials in which dietary advice was given together with other interventions reduced the number of subjects available for analysis. However, limiting the overview to single interventions may provide a better estimate of the effect of dietary advice by increasing the likelihood that dietary messages were delivered without dilution by other forms of health advice. In addition, this approach had the advantage that the estimate of the effect of dietary advice was largely unconfounded by other interventions which might affect cholesterol values such as exercise and substantial weight loss. The low fat diets were associated with significant weight loss (2-3 kg), and this may contribute to some of the cholesterol lowering—for example, a weight loss of 1 kg is associated with a reduction in cholesterol concentration of 0.05 mmol/l.[7] However, weight loss was minimal in most of the other trials included in this overview and so is unlikely to account for much of the reduction in cholesterol concentration.

Our inclusion of only randomised and unconfounded comparisons may partly explain the smaller reductions in cholesterol concentration in comparison with some previous reviews.[14]

Two other methodological limitations of the present overview need to be borne in mind: the possibility of publication bias[54] and the use of tabulated data derived from published reports.[55] Although we tried to minimise publication bias, we were not able to identify any unpublished trials. In addition, unpublished trials might exist that would have been eligible for this review and, with only one person reviewing all the published reports of potential trials, some published trials may also have been missed. As studies with negative results are less likely to be published, the probable effect would be to further reduce our summary estimates of effectiveness. We tried to address some of the shortcomings of limiting our analysis to published tabulated data by approaching investigators and experts in the subject to obtain additional unpublished data for their studies or to clarify areas of uncertainty, but this was largely unsuccessful.

**Key messages**

- Results from metabolic ward studies suggest that dietary change can reduce blood cholesterol concentrations by up to 15%
- In free-living subjects the standard step 1 diet of the American Heart Association lowers cholesterol concentration by about 3%, and about another 3% can be achieved with more intensive diets
- Difficulties in complying with the prescribed dietary change explain the failure to achieve the expected reductions in cholesterol concentrations
- It is important to be realistic about the reductions in cardiovascular risk that can be achieved by individual dietary counselling

**Conclusions**

This systematic review suggests that dietary advice to free-living subjects can be expected to reduce blood total cholesterol by only 3-6%, depending on the type and intensity of the diet advocated. In particular, the step 1 diet of the American Heart Association has only a small cholesterol lowering effect even among those with evidence of coronary disease. Our analyses relate to effects on blood total cholesterol concentration, and diets that simply lower total fat intake may lower high density lipoprotein cholesterol concentration and offset beneficial effects on coronary heart disease from lowering low density lipoprotein cholesterol.[3] This is less likely to be the case with diets in which reduction in saturated fat is replaced by polyunsaturated and monounsaturated fats rather than by complex carbohydrates. The limited efficacy of dietary advice alone should be taken into account in routine clinical practice and when assessing the cost effectiveness of different preventive strategies. More research is required to develop better methods of communicating dietary advice and maintaining compliance with such advice. Small changes in population blood total cholesterol concentrations may be worth while, but this may be better achieved by interventions aimed at populations than by advising individual people about diet.

We acknowledge the help of Simon Wilson and Paul Sherliker in preparing the original figure, and we thank Robert Clarke for his helpful comments about the manuscript.

JLT searched the databases for relevant papers, extracted the data from identified studies, performed most of the statistical analyses, and contributed to writing the manuscript. JMA initiated and coordinated the project, extracted data from the identified trials independently, wrote the manuscript, prepared the table, coordinated contributions from other authors, and performed some of the statistical analyses. TL was on the steering group for the project, discussed core ideas, and helped prepare the manuscript. CAS initiated the project, helped in designing and writing up the study protocol, discussed core ideas, and helped prepare the manuscript. GHF was on the steering group of the project and participated in the design and execution of the project. HAWN initiated the project, wrote the grant application for funding from the Department of Health, was on the steering group, discussed core ideas, and helped prepare the manuscript.

Funding: The study was funded by a project grant from the nutrition programme phase 1 of the Department of Health and Medical Research Council. JMA is supported by the British Heart Foundation. TL is supported by the Imperial Cancer Research Fund. The Clinical Trial Service Unit and Epidemiological Studies Unit receives funding from the Medical Research Council, British Heart Foundation, and Imperial Cancer Research Fund.

Conflict of interest: None.

1 Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. *Lancet* 1986;2:933-6.
2 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.
3 Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: a quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;314:112-7.
4 Hegsted DM, Ausman LM, Johnson JA, Dallal GE. Dietary fat and serum lipids: an evaluation of the experimental data. *Am J Clin Nutr* 1993;57:875-83.
5 Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 1965;17:281-95.
6 Keys A, Anderson JT, Grande F. Prediction of serum cholesterol responses of man to changes in fat in the diet. *Lancet* 1957;ii:959-66.
7 Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;56:320-8.
8 Ripsin CM, Keenan JM, Jacobs DR Jr, Elmer PJ, Welch RR, Van Horn L, et al. Oat products and lipid lowering: A meta-analysis. *JAMA* 1992;267:3317-25.
9 Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Phys Lond* 1994;28:39-45.
10 Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. *J Lipid Res* 1989;30:785-807.
11 Secretary of State for Health. *The health of the nation: a strategy for health in England*. London: HMSO, 1992. (Cm 1986.)
12 Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med* 1988;148:36-69.
13 Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. *BMJ* 1991;303:953-7.
14 Denke MA. Cholesterol-lowering diets. A review of the evidence. *Arch Intern Med* 1995;155:17-26.
15 Bracken MB. Statistical methods for analysis of effects of treatment in overviews of randomised trials. In: Sinclair JC, Bracken MB, eds. *Effective care of the new-born infant*. Oxford: Oxford University Press, 1992:13-8.
16 Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992;45:769-73.
17 Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* 1994;309:1351-5.
18 Neil HA, Roe L, Godlee RJP, Moore JW, Clark GMG, Brown J, et al. Randomised trial of lipid lowering dietary advice in general practice: the effects on serum lipids, lipoproteins, and antioxidants. *BMJ* 1995;310:569-73.
19 Rivellese AA, Auletta P, Marotta G, Saldalamacchia G, Giacco A, Mastrilli V, et al. Long term metabolic effects of two dietary methods of treating hyperlipidaemia. *BMJ* 1994;308:227-31.
20 Duffield RG, Lewis B, Miller NE, Jamieson CW, Brunt JN, Colchester AC. Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis. A randomised controlled trial. *Lancet* 1983;2:639-42.
21 Johnston HJ, Jones M, Ridler Dutton G, Spechler F, Stokes GS, Wyndham LE. Diet modification in lowering plasma cholesterol levels. A randomised trial of three types of intervention. *Med J Aust* 1995;162:524-6.
22 Kromhout D, Arntzenius AC, van der Velde EA. Diet and coronary heart disease: the Leiden intervention trial. *Bibl Nutr Dieta* 1986;37:119-20.
23 Reid CM, Dart AM, Dewar EM, Jennings GL. Interactions between the effects of exercise and weight loss on risk factors, cardiovascular haemodynamics and left ventricular structure in overweight subjects. *J Hypertens* 1994;12:291-301.
24 Curzio JL, Kennedy SS, Elliott HL, Farish E, Barnes JF, Howie CA, et al. Hypercholesterolaemia in treated hypertensives: A controlled trial of intensive dietary advice. *J Hypertens* 1989;7:S254-5.
25 Koopman H, Spreeuwenberg C, Westerman RF, Donker AJ. Dietary treatment of patients with mild to moderate hypertension in a general practice: a pilot intervention study. I. The first three months. *J Hum Hypertens* 1990;4:368-71.
26 Jalkanen L. The effect of a weight reduction program on cardiovascular risk factors among overweight hypertensives in primary health care. *Scand J Soc Med* 1991;19:66-71.
27 MacMahon S, Macdonald G. Treatment of high blood pressure in overweight patients. *Nephron* 1987;47 (suppl 1):8-12.
28 Marniemi J, Seppanen A, Hakala P. Long-term effects on lipid metabolism of weight reduction on lactovegetarian and mixed diet. *Int J Obes* 1990;14:113-25.
29 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaund I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9. [Erratum appears in *Lancet* 1995;345:738.]
30 Singh RB, Rastogi SS, Sircar AR, Mehta PJ, Sharma KK. Dietary strategies for risk-factor modification to prevent cardiovascular diseases. *Nutrition* 1991;7:210-4.
31 Buzzard IM, Asp EH, Chlebowski RT, Boyar AP, Jeffrey RW, Nixon DW, et al. Diet intervention methods to reduce fat intake: nutrient and food group composition of self-selected low-fat diets. *J Am Diet Assoc* 1990;90:42-50, 53.
32 Demark-Wahnefried W, Bowering J, Cohen PS. Reduced serum cholesterol with dietary change using fat-modified and oat bran supplemented diets. *J Am Diet Assoc* 1990;90:223-9.
33 Bloemberg BPM, Kromhout D, Goddijn HE, Jansen A, Obermann de Boer GL. The impact of the guidelines for a healthy diet of the Netherlands Nutrition Council on total and high density lipoprotein cholesterol in hypercholesterolemic free-living men. *Am J Epidemiol* 1991;134:39-48.
34 Sarkkinen ES, Uusitupa MI, Pietinen P, Aro A, Ahola I, Penttila I, et al. Long-term effects of three fat-modified diets in hypercholesterolemic subjects. *Atherosclerosis* 1994;105:9-23.
35 Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-61.
36 Sciarrone SEG, Beilin LJ, Rouse IL, Rogers PB. A factorial study of salt restriction and a low-fat/high-fibre diet in hypertensive subjects. *J Hypertens* 1992;10:287-98.
37 Anonymous. The national diet-heart study final report. *Circulation* 1968;37:I1-428.
38 Ehnholm C, Huttunen JK, Pietinen P, Leino U, Mutanen M, Kostiainen E, et al. Effect of diet on serum lipoproteins in a population with a high risk of coronary heart disease. *N Engl J Med* 1982;307:850-5.
39 Baron JA, Gleason R, Crowe B, Mann JI. Preliminary trial of the effect of general practice based nutritional advice. *Br J Gen Pract* 1990;40:137-41.
40 Watts GF, Lewis B, Brunt JNH, Lewis ES, Coltart DJ, Smith LDR, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' atherosclerosis regression study (STARS). *Lancet* 1992;339:563-9.
41 Hunninghake DB, Stein EA, Dujovne CA, Harris WS, Feldman EB, Miller VT, et al. The efficacy of intensive dietary therapy alone or combined with lovastatin in outpatients with hypercholesterolemia. *N Engl J Med* 1993;328:1213-9.
42 Anderson JW, Garrity TF, Wood CL, Whitis SE, Smith BM, Oeltgen PR. Prospective, randomised, controlled comparison of the effects of low- fat and low-fat plus high-fiber diets on serum lipid concentrations. *Am J Clin Nutr* 1992;56:887-94.
43 Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The dietary intervention study in children (DISC). *JAMA* 1995;273:1429-35.
44 Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation* 1970;42:935-42.
45 Leren P. The effect of plasma-cholesterol-lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Bull N Y Acad Med* 1968;44:1012-20.
46 Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Med Scand Suppl* 1966;466:1-92.
47 Woodhill JM, Palmer AJ, Leelarthaepin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol* 1978;109:317-30.
48 Kuusi T, Ehnholm C, Huttunen JK, Kostiainen E, Pietinen P, Leino U, et al. Concentration and composition of serum lipoproteins during a low-fat diet at two levels of polyunsaturated fat. *J Lipid Res* 1985;26:360-7.
49 Dreon DM, Vranizan KM, Krauss RM, Austin MA, Wood PD. The effects of polyunsaturated fat vs monounsaturated fat on plasma lipoproteins. *JAMA* 1990;263:2462-6.
50 Research Committee. Low-fat diet in myocardial infarction: A controlled trial. *Lancet* 1965;2:501-4.
51 Insull W Jr, Henderson MM, Prentice RL, Thompson DJ, Clifford C, Goldman S, et al. Results of a randomised feasibility study of a low-fat diet. *Arch Intern Med* 1990;150:421-7.
52 Boyd NF, Cousins M, Beaton M, Fishell E, Wright B, Fish E, et al. Clinical trial of low-fat, high-carbohydrate diet in subjects with mammographic dysplasia: report of early outcomes. *J Natl Cancer Inst* 1988;80:1244-8.
53 Gregory J, Foster K, Tyler H, Wiseman M. *The dietary and nutritional survey of British adults*. London: HMSO, 1990.
54 Simes RJ. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* 1986;4:1529-41.
55 Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;341:418-22.

*(Accepted 23 September 1997)*

# Commentary: Dietary change, cholesterol reduction, and the public health—what does meta-analysis add?

George Davey Smith, Shah Ebrahim

Department of Social Medicine, Canynge Hall, Bristol BS8 2PR
George Davey Smith, *professor of clinical epidemiology*

Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London NW3 2PF
Shah Ebrahim, *professor of clinical epidemiology*

Dietary changes *can* lead to sizeable reductions in circulating cholesterol concentrations,[1] which would translate into meaningful decreases in morbidity and mortality from coronary heart disease. The dietary manipulations which have produced substantial lowering have, however, been implemented in strictly controlled conditions in volunteers living in institutions, whose food intake is directly regulated. Animal experimentation and metabolic ward studies carried out over half a century show that we should not be surprised by substantial declines in cholesterol concentration in someone who is locked in a room and fed lettuce. The results of studies with externally regulated dietary intake have, inappropriately, been taken to be directly translatable into public health terms—for example, a review of metabolic ward studies has been cited as an apparent refutation of scepticism about the ability to modify cholesterol concentrations in the general population by diet.[2] This is extrapolating well beyond what the studies show: to understand what could be produced in real life settings by dietary interventions requires studies which have attempted to produce sustained changes in the diet of subjects who continue living their lives.

When dietary interventions are implemented in community settings the outcomes may differ from expectation. Firstly, compliance with dietary advice may be poor—people eat particular foods because they are easily available and affordable and they like them, not because of ignorance or a death wish. Thus the dietary changes produced by an intervention—and the consequent decline in serum cholesterol concentration—may be considerably less than anticipated. Secondly, outside metabolic wards, diets consist of complex and changing mixtures of food, whose individual elements may interact—either behaviourally or biologically—to produce different effects from those that occur when single dietary components are manipulated.

There have been several quantitative and semi-quantitative reviews of trials of dietary interventions in real world settings,[3 4] of which the paper by Tang et al is the latest. The differences between these analyses illustrate the problems of meta-analyses of complex interventions. In particular, the inclusion criteria are difficult to define. What kind of intervention counts as "global dietary modification" (and thus is included by Tang et al) rather than a single component intervention (and thus excluded)? What constitutes "specific supplementation" of the diet (and is thus excluded)? It is difficult to make these criteria objective and reproducible—Tang et al have included only four of the 10 trials included in a previous meta-analysis,[4] and in many of these cases it is not clear from differences in inclusion criteria why this is so.

A striking finding of the reviews of real life dietary intervention trials is the great variation seen in the effects produced in different studies. Even with a weak test, formal statistical analysis yields substantial heterogeneity between the studies, and in this case the combination of results should be cautiously applied, if at all. It is more useful to look at differences between studies to identify elements of the intervention or characteristics of the study group which may account for the variation. This was the case in our recent meta-analysis of multiple risk factor intervention studies, in which the differences between studies is in some ways more informative than the pooled effect.[5]

For public health purposes the bottomline findings of reviews and meta-analyses of single factor and multifactorial interventions[3–5] is that even with the substantial resources given to changing people's diets the resulting reduction in cholesterol concentrations is disappointing. General population health education campaigns (or health promotion programmes, as they tend to be called now) are of limited effectiveness. Health protection—through legislative and fiscal means—is likely to be a better investment.

1 Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: a quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;314:112-7.
2 Marmot M. The cholesterol papers. *BMJ* 1994;314:112-7.
3 Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. *BMJ* 1991;30:953-7.
4 Brunner E, White I, Thorogood M, Bristow A, Curle D, Marmot M. Can dietary interventions in the population change diet and cardiovascular risk factors? An assessment of effectiveness utilising a meta-analysis of randomised controlled trials. *Am J Public Health* 1997;87:1415-22.
5 Ebrahim S, Davey Smith G. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *BMJ* 1997;314:1666-74.

*Fifty years ago*

## The new NHS: Medical students say no

SIR—I am amazed how little consideration has been given to the opinions of tomorrow's doctors. We medical students must stand by and watch others decide our future. We place all our hope in the good sense of those who are to vote in a few days' time. Let them remember that it is not merely their own private interests which are at stake, but the freedom of thousands of would-be doctors who have no say in the matter at all. If doctors accept the State Medical Service as it stands, with its many good points but several entirely unacceptable ones, they will condemn us to a life of State service which we had not bargained for when we took up medicine. If they do but stand firm, they can insist on a form of service which they would not be ashamed to hand on to us.—I am, etc, Peter Lyne, Cambridge. (*Letter*, 31 January 1948, p 215. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)