European Heart Journal Supplements (2001) **3** (*Supplement D*), D79–D84

Dietary fats in the prevention of coronary heart disease: the need for more clinical trials

T. D. Barringer

Carolinas Health Care System, Department of Family Practice, CHC-MP Building, P.O. Box 32861, Charlotte, NC 28232, U.S.A.

On the basis of various lines of evidence, including clinical trials, diet appears to have the potential to lessen the risk of CHD events, independent of effects on serum lipid values, at least as great as the most effective medical and interventional treatments available today. Given the diversity of these cardioprotective diets, as well as their salutary components, one of the priorities in research should be to undertake more comparative trials, trials which determine patient acceptability, effects on surrogate markers of risk, and which ultimately impact on morbidity and mortality.

The Carolina Diet Heart Trial is a clinical outcome trial comparing two 'proven' cardioprotective diets, the AHA endorsed Step II diet versus an American–Mediterranean diet, and having the amount and type of unsaturated fat as the main dependent variable. This study is a prospective, randomized, multi-centre, secondary prevention trial with the ultimate intention of reducing the incidence of subsequent cardiovascular events through dietary modification in patients who have survived a previous acute coronary syndrome. The study intervention is also designed to give these patients the necessary knowledge, motivation and practical ability to modify their current diets and maintain long-term adherence to a more cardioprotective diet. The initial pilot phase will assess compliance with the two study diets, as well as assess the impact of each diet on a marker of CHD risk.
(Eur Heart J Supplements 2001; 3 (Suppl D): D79–D84)

Key Words: n-3 fats, Mediterranean diet, whole dietary pattern.

Introduction

The best diet for the prevention of coronary heart disease (CHD) is unknown. Supported by animal experiments and large cohort studies, clinical outcome dietary trials have basically established that restricting saturated fat intake while substituting polyunsaturated fats will lower the risk of CHD roughly proportional to the degree of serum cholesterol lowering[1,2]. This data forms the basis of the American Heart Association (AHA) and European recommendations for diet in secondary prevention, which are nearly identical and summarized by restrictions in fat intake: total fat <30% of total calories, saturated fat <7%, and cholesterol <200 mg . day^{-1}[3,4]. There are two main reasons, however, why this approach to the dietary prevention of CHD may no longer be valid.

First, statin therapy is far more powerful in both cholesterol-lowering effectiveness and in reduction of CHD morbidity and mortality[5,6,7]. All of the clinical outcome trials establishing the clinical effectiveness of saturated fat restriction with polyunsaturated fat substitution were conducted long before the era of statins, as were other highly effective pharmacological therapies used in prevention[8–10]. There is no evidence that any additional benefit is derived by adhering to such a diet in this context. Two more recent multi-interventional trials have shown that the combination of a low-fat, high- carbohydrate diet plus modification of traditional risk factors (e.g. hypertension, smoking, etc.) reduces angiographic progression of coronary disease and hospital admission for coronary events, but it is impossible to distinguish the contribution of the dietary changes to this success[11,12].

Secondly, ever since early ecological observations revealed that certain ethnic populations have very low rates of CHD in spite of relatively high fat consumption[13,14], evidence has been accumulating that some diets are cardioprotective independent of a major effect on serum cholesterol. Three clinical trials have been undertaken in recent years which have tested whether presumed cardioprotective diets can reduce the risk of cardiac events in populations with known CHD.

Cardioprotective diet trials

The first of these was the Diet and Reinfarction Trial (DART), which compared three diets: a low saturated fat diet plus increased polyunsaturated fats, a high fish

Correspondence: Thomas D. Barringer. Address as above.

1520-765X/01/0D0079+06 $35.00/0

diet (requiring at least two portions of fatty fish or fish oil supplements per week), and a high-fibre diet. Only the group given fish advice had a significant reduction in CHD deaths; overall mortality was reduced 29% after 2 years, although there was a non-significant increase in myocardial infarction rates[15].

In the Indian Diet Heart Study[16], a low-fat diet (approximately 28% of the total calories) was compared with an even lower-fat diet (approximately 24% of the total calories) combined with an increased intake of fruits, vegetables, pulses, nuts and fish. Patients were randomized within 48 h of a suspected myocardial infarction; CHD events were reduced in the intervention group after only 6 weeks. At 1 year, there was a 42% reduction in cardiac deaths and a 45% reduction in total mortality.

The Lyon Diet Heart Study[17], which had the largest effect size and provided the most analytical detail, compared a 'prudent Western-type diet' with a 'Mediterranean-type diet'. The latter was defined as 'more bread, more root vegetables and green vegetables, more fish, less meat, no day without fruit, and butter and cream to be replaced with margarine supplied by the study', which was canola-oil-based (chosen because it is higher in alpha-linolenic acid than other oils). After a mean follow-up of 27 months, there was a 73% reduction in cardiac deaths and non-fatal myocardial infarction. Overall mortality was reduced by 70%. This effect did not diminish significantly when the final follow-up data was analyzed at 4 years[18].

All three of these dietary trials were remarkably successful in reducing CHD events. However, the multiple and complex dietary changes implemented do not permit conclusions about which specific components of these diets are most beneficial, whether certain food or nutrient combinations are critical, and what difference the usual dietary patterns of the particular populations studied had on outcome. Nevertheless, these studies lay the foundation for further studies of cardioprotective diets, and stress the importance of other dietary factors besides saturated fat and cholesterol intake.

Fish, fish oils and n-3 fatty acids

Unlike the Indian and Lyon trials, the dietary intervention in DART was mono-factorial, namely higher fish/fish oil intake. Some[19–21] but not all[22–24], of the epidemiological studies addressing this question show an inverse correlation between CHD mortality and fish consumption. One explanation offered for this discrepancy is the variable baseline fish intake of the populations studied, with greater benefit derived for those groups with little to no regular fish consumption. The recently published GISSI–Prevenzione trial investigated the effects of fish oil capsules (providing approximately 850 mg of EPA plus DHA) in patients with recent myocardial infarction. This supplementation resulted in a 15% reduction in the combined end-point of death, non-fatal MI and non-fatal stroke, and a 20% reduction in total mortality after 3·5 years[25]. Sudden cardiac death specifically was reduced by 45% in the fish oil supplemented group. The latter effect is supported by various experimental studies in animals which have shown an antiarrhythmic effect of n-3 fatty acids[26,27]. Baseline fish consumption was quite high in all groups.

In the Lyon Diet Heart Study the authors propose that the most critical nutrient component was the higher intake of alpha-linolenic acid in the experimental group. Several large observational studies support this contention, having revealed a strong inverse association for alpha-linolenic acid and CHD mortality[28–30].

Nevertheless, it cannot be assumed without further evidence that the benefit of these cardioprotective diets derives primarily from the increase in n-3 fatty acid consumption. For example, in the Lyon Diet Heart Study, the experimental diet group consumed less total fat (30·5% versus 32·7% of total calories), less saturated fat (8·3% versus 11·7%), less cholesterol (217 mg . day^{-1} versus 318 mg . day^{-1}), less linoleic acid (3·6% versus 5·3%), more alpha-linolenic acid (0·81% versus 0·27%), and more oleic acid (12·9% versus 10·3%). Diets in the Indian and Lyon trials were also characterized by higher intakes of fresh fruits, vegetables, legumes and cereals, which increased the amount of whole-grain, fibre, natural antioxidants (e.g. polyphenols such as flavonoids), minerals, arginine (an amino acid with major effects on vascular and platelet function[31,32], and B vitamins. Support for the cardioprotective benefit of these 'other' ingredients comes from numerous recent observational trials, which have indicated strong inverse associations between CHD incidence and consumption of whole-grain[33,34], fibre[35,36], nuts[37–40], fruits and vegetables[41–43], folate[44], vitamin B_6[44], and flavonoids[45–47]. The effect of a similar low-fat whole dietary pattern was recently assessed in a large cohort study using a 'recommended food score'. This score was based on how often an individual ate foods from a list of fruits, vegetables, whole grains, low-fat milk and lean meats and poultry. No foods high in n-3 fatty acids were included in the calculation. Those women in the highest quartile compared with those in the lowest had a relative risk of CHD of 0·67, a relative risk of cancer of 0·60, and an all-cause mortality relative risk of 0·69 over a median follow-up period of 5·6 years[48].

Future dietary trials

This brief overview highlights the fact that various constituents in diet are detrimental and even more are protective, in regard to coronary heart disease, but that most of these associations have not been tested in clinical outcome trials. It is certainly not feasible to study each component in separate intervention trials, nor would it necessarily provide accurate or practical information, since nutrients are consumed as part of a whole diet and may be dependent upon one another in having their most salutary effects. Therefore, whole dietary patterns which already have some evidence for

being cardioprotective need to continue to be compared in metabolic studies and clinical trials. Specific issues, such as the clinical benefits of n-3 fats, must still be addressed in such whole-diet trials, while leaving the precise mechanism questions to be resolved in the laboratory. Studying different populations is essential as this variable may corroborate, or confound, results. For example, replicating the Lyon trial in the U.S.A. (or the U.K., northern Europe or Australia), would inevitably entail differences in the Mediterranean diet compared with southern France. However, comparable results would confirm the importance of the quantitative component of the nutrients being studied, while null results would highlight the importance of the qualitative differences, among other variables.

An American–Mediterranean dietary trial

In the U.S.A. the AHA and National Cholesterol Education Program Step II guidelines for fat intake have served as the starting point for recommendations made by physicians and dieticians to CHD patients for years (see the Introduction of this article). Most dieticians are providing further advice supported by nutritional research regarding the detrimental and cardioprotective effects of other nutrients (e.g. trans fatty acids, wholegrain, fibre, fish, fruit and vegetables). Many are presenting a 'hybrid' diet, trying to incorporate information on the benefits of n-3 fats and possibly monounsaturated fats, while restricting total fat in line with AHA guidelines, sometimes resulting in specific dietary recommendations that are incompatible. Some are 'tailoring' their advice according to the lipid profiles of patients. All of these approaches are understandable, but the confusion and lack of consistency is lamentable, and only weakens confidence and compliance with any advice. The solution is a clinical outcomes trial comparing two 'proven' cardioprotective diets, the AHA endorsed Step II diet versus an American–Mediterranean diet, with the main dependent variable being the amount and type of unsaturated fat. Even null results would allay patient and clinician anxieties and confusion over how much and which fats to recommend.

Clinical outcome trials, superior as they are in the hierarchy of evidence, are difficult and expensive. Before an adequate one could be conducted, a pilot trial would be necessary to prove feasibility, specifically that an American population can maintain long-term adherence to both diets. Knowledge, beliefs, cost, convenience and palatability are obvious issues to be addressed in achieving the necessary dietary changes; any difference in compliance would nonetheless help to determine which of these factors are most important and provide information useful in advising individual patients.

A pilot study could also further support the biological plausibility of a major clinical benefit from diet if reliable, strong surrogate markers of risk were positively impacted. As already mentioned, the cardioprotective dietary trials with the most dramatic reduction in CHD events had no significant impact on serum lipid values. Therefore, the primary mechanism of such a powerful effect remains speculative, even if it were determined to be related to the n-3 fat intake. Atherosclerosis, however, is more than a dislipidaemia aberration. Accumulating evidence suggests it is also an inflammatory disease[49]. Given that n-3 fatty acids have potent anti-inflammatory properties[50], a reasonable hypothesis is that the success achieved in the Lyon trial was due to this mechanism. One of the best markers of inflammation, C-reactive protein, is also currently one of the strongest and most reliable markers of CHD risk[51,52]. C-reactive protein therefore would be an ideal surrogate marker in a Mediterranean (high n-3 fatty acid) dietary trial. I have outlined what I think would be the necessary steps in making further progress toward understanding the role of diet in general, and n-3 fats in particular, in the prevention of CHD. We, at Carolinas Medical Center, have started taking these step with a pilot trial, and hope to lay the foundation for a subsequent clinical outcomes trial.

The Carolina diet heart study

Study design

This study is a prospective, randomized, multicentre, secondary prevention trial with the ultimate intention of reducing the incidence of subsequent cardiovascular events through dietary modification in patients who have survived a previous acute coronary syndrome. The study intervention is also designed to give these patients the necessary knowledge, motivation, and practical ability to modify their current diets and maintain long-term adherence to a more cardioprotective diet. The initial pilot phase will assess compliance to the two study diets, as well as assess impact of each diet on a marker of CHD risk.

Population and duration

The pilot trial will enrol 144 patients of either sex, recruited from the participating cardiac rehabilitation centres over approximately 6 months. Patients will be followed for at least 6 months, for a total trial duration of 12 months.

Inclusion criterion

All patients must be 35–75 years old, and have a history of an acute coronary syndrome (myocardial infarction or unstable angina) or revascularization within 3 months of enrolment. They also must have the physical and mental ability to participate in a comprehensive cardiac rehabilitation programme, as judged by the referring

Table 1 Specific contents of Step II and Mediterranian diets in the Carolina Diet Heart Trial

	Step II	Mediterranean	AAD†
Total fat (% of total calories)*	30%	34%	34%
Saturated (% total calories)	<7%	<7%	16%
Polyunsaturated (% total calories)	<10%	<10%	7%
n-6/n-3 ratio*	na	4	10
Alpha-linolenic acid (g . day^{-1})*	na	≥2 g	1·2 g
EPA+DHA (mg . day^{-1})*	na	≥650 mg	200 mg
Monounsaturated (% total calories)*	10–15%	10–20%	11%
Trans fatty acids (% total calories)	<1·3%	<1·3%	2·6%
Cholesterol (mg . day^{-1})*	<200 mg	<300 mg	400 mg
Carbohydrate (% total calories)	≥50%	≥45%	50%
Protein (% total calories)	10–20%	10–20%	16%
Fibre (g . day^{-1})	20–35 g	20–35 g	15 g
Total calories	To achieve and maintain desirable body weight		

*Designated differences.
†AAD=average American diet for comparison purposes.

physician, the medical director of the programme, and by standard pre-entry criteria of the particular cardiac rehabilitation programme (e.g. exercise testing, ambulatory EKG monitoring).

Exclusion criteria

Criteria for exclusion include not meeting eligibility criteria for participation in the cardiac rehabilitation programme, uncontrolled hypertension (systolic >160 mmHg, diastolic >100 mmHg), or an inability to perform an exercise test due to recurrent angina, ventricular arrhythmia or high-grade AV block, or evidence of an unstable condition manifested during exercise testing (e.g. hypotension, syncope, severe ischaemic EKG changes).

Recruitment and enrolment

Consecutive patients who have survived an acute coronary syndrome in the previous 3 months and who are starting one of the participating cardiac rehabilitation programmes will be invited to participate by agreeing to be randomized to one of two diets. Both diets will be explained verbally and in written format in the informed consent. Patients will then be given 1–2 weeks to decide before their first appointment with the dietician. Each study site will have one dietician teaching both of the diets being compared in this trial in order to avoid the differential impact of the dieticians own personality and teaching success in achieving dietary compliance.

Diet intervention

Each patient (with spouse or other similar person instrumental in food selection) will attend an initial session with the dietician to receive detailed instructions in how to adhere to their particular diet. The specific content of the two diets is given in Table 1 (with designated differences in shown with an asterisk): In order to decrease the n-6/n-3 ratio in the Mediterranean group, consumption of foods naturally high (or fortified) in n-3 fatty acids (e.g. fatty fish, canola-oil-based spreads, flaxseed oil and flour, n-3 fortified eggs, walnuts), will be specifically advised, and ongoing assistance provided in how to incorporate these foods into the diet. Fatty fish will be advised at least twice weekly. A canola-oil-based margarine will be recommended to these patients as well. To increase the monounsaturated fat intake, olive and canola oils exclusively will be recommended for salads and food preparation, and nut consumption 1/2–1 oz . day^{-1} will be advised.

Compared with the average American diet, both groups will receive education and instruction in using:

more—
- whole-grain and fibre (e.g. whole grain breads and cereals, at least two servings per day);
- fruits and vegetables (five to nine portions combined per day), and;

less—
- saturated fat (<7% of total daily calories);
- trans fatty acids (<1·3% of total daily calories);
- cholesterol and total fat (though the Mediterranean group will have a slightly higher allowance in order to accommodate the increased consumption of foods higher in n-3 and monounsaturated fats).

This verbal instruction will be reinforced with written material given to the patient at the time of their initial meeting with the dietician.

After the initial dietary instruction, adherence to the diets will be supported by:

(1) a follow-up visit with the dietician individually at 8 weeks to address individual problems with adherence

revealed on the food-frequency questionnaire at 6 weeks;
(2) bi-monthly newsletters, consisting of practical, educational, and motivational material designed to enhance compliance;
(3) educational group meetings three times in the first year, each consisting of recipe tasting, an educational lecture with question and answer session and group sharing.

Data collection

Demographic and baseline characteristics will be obtained consisting of age, sex, marital status, smoking history, infarction history, other medical diagnoses (including diabetes mellitus, hypertension, heart failure, atrial fibrillation and stroke history), surgical history (including coronary artery bypass grafting and angioplasty procedures), all medications (including vitamins and herbals) and family history of premature CHD. Weight, body mass index (BMI), blood pressure, and fasting lipid profile will be obtained at baseline and again at 6 months. Baseline dietary habits will be assessed by administration of a food-frequency questionnaire (the Harvard 96GP) at entry into the study.

Compliance with the study diets will be determined by the same food-frequency questionnaire at 6 months, and by RBC membrane fatty acid analysis obtained at baseline and 6 months.

Clinical event information will be ascertained from patients at all office visits, and by return of a self-addressed postcard enclosed in the bimonthly newsletters, which will be followed up with a phone call.

Outcome assessment

The primary end-points of the pilot trial are the mean intakes and the percentage of patients achieving the goal intake in each designated food or nutrient category (e.g. total fat, whole-grain, fibre, alpha-linolenic acid, EPA+DHA, n-6/n-3 ratio).

The primary clinical end-points are cardiac death, non-fatal myocardial infarction and total mortality. Secondary clinical end-points are unstable angina, heart failure, stroke, pulmonary or peripheral embolism, and revascularization procedures. Documentation will come from hospital discharge summaries or death certificates. Validation of clinical events will be assured by an ad hoc committee of cardiologists or neurologists blinded to the patients' dietary assignment.

Summary

On the basis of various lines of evidence, including clinical trials, diet appears to have a potential to lessen the risk of CHD events, independent of effects on serum lipid values, at least as great as the most effective medical and interventional treatments available today. Given the diversity of these cardioprotective diets, as well as their salutary components, one of the priorities in research should be to undertake more comparative trials, trials which determine patient acceptability, effects on surrogate markers of risk, and which ultimately impact on morbidity and mortality.

References

[1] Sacks F. Dietary fats and coronary heart disease. Overview. J Cardiovasc Risk 1994; 1: 3–8.
[2] Truswell AS. Review of dietary intervention studies: effect on coronary events and mortality. Aust NZ J Med 1994; 24: 308–15.
[3] Consensus Panel. Statement. Preventing heart attack and death in patients with coronary disease. Circulation 1995; 92: 2–4.
[4] Pyorala K, de Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 1994; 15: 1300–31.
[5] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.
[6] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333: 1301–7.
[7] LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease; a meta-analysis of randomised controlled trials. J Am Med Assoc 1999; 282: 2340–6.
[8] Dayton S, Pierce ML, Hashimoto S *et al*. A controlled clinical trial of a diet high in unsaturated fat preventing complications in atherosclerosis. Circulation 1969; 39/40 (Suppl II): 63.
[9] Leren P. The Oslo Diet-Heart Study. Eleven-year report. Circulation 1970; 42: 935–42.
[10] Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: The Finnish Mental Hospital Study. Int J Epidemiol 1979; 8: 99–118.
[11] Haskell WL, Alderman EL, Fair JM *et al*. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: the Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994; 89: 975–90.
[12] Ornish D, Scherwitz L, Billings J *et al*. Intensive lifestyle changes for reversal of coronary heart disease. J Am Med Assoc 1998; 280: 2001–7.
[13] Keys A. Seven Countries: a multivariate analysis of death and coronary heart disease. Cambridge, MA: Harvard University Press, 1980.
[14] Bang HO, Dyerberg J, Hjorne N. The composition of food consumed by Greenland Eskimos. Acta Med Scand 1976; 200: 69–73.
[15] Burr ML, Fehily AM, Gilbert JF *et al*. Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). Lancet 1989; ii: 757–61.
[16] Singh RB, Rastogi SS, Verma R *et al*. Randomised controlled trial of cardioprotective diet in patients with acute myocardial infarction: results of one year follow-up. Br Med J 1992; 304: 1015–9.
[17] de Lorgeril M, Renaud S, Mamele N *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994; 343: 454–9.

[18] de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999; 99: 779–85.
[19] Kromhout D, Bosschieter EB, de Lezenne CC. The inverse relationship between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985; 312: 1205–9.
[20] Daviglus ML, Stamler J, Orencia AJ *et al*. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997; 336: 1046–53.
[21] Shekelle RB, Stamler MJ. Fish and coronary heart disease: the epidemiological evidence. Nutr Metab Cardiovas Dis 1993; 4: 46–51.
[22] Albert CM, Hennekens CH, O'Donnell CJ *et al*. Fish consumption and risk of sudden cardiac death. J Am Med Assoc 1998; 279: 23–8.
[23] Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake and the risk of coronary disease among men. N Engl J Med 1995; 332: 977–82.
[24] Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH. Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study. Am J Epidemiol 1995; 142: 166–75.
[25] GISSI–Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI–Prevenzione trial. Lancet 1999; 354: 447–55.
[26] Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. Circulation 1996; 94: 1774–80.
[27] Billman GE, Kang JX, Leaf A. Prevention of ischemia-induced ventricular arrhythmias by dietary pure n-3 polyunsaturated fatty acids in dogs. Circulation 1996; 99: 2452–7.
[28] Hu FB, Stampfer MJ, Manson JE *et al*. Dietary intake of a-linolenic acid and risk of fatal ischaemic heart disease among women. Am J Clin Nutr 1999; 69: 890–7.
[29] Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. Proc Soc Exp Biol Med 1992; 200: 177–82.
[30] Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. Br Med J 1996; 313: 84–90.
[31] Cooke JP. Is atherosclerosis an arginine deficiency disease? J Invest Med 1998; 46: 377–80.
[32] De Lorgeril M. Dietary arginine and the prevention of cardiovascular diseases. Cardiovasc Res 1998; 37: 560–3.
[33] Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischaemic heart disease death in postmenopausal women: the Iowa Women's Health Study. Am J Clin Nutr 1998; 248–57.
[34] Liu S, Stampfer MJ, Hu FB *et al*. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999; 70: 412–9.
[35] Pietinen P, Rimm EB, Korhonen P *et al*. Intake of dietary fibre and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Circulation 1996; 94: 2720–7.
[36] Wolk A, Manson JE, Stampfer MJ *et al*. Long-term intake of dietary fibre and decreased risk of coronary heart disease among women. J Am Med Assoc 1999; 281: 1998–2004.
[37] Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease: the Adventist Health Study. Arch Intern Med 1992; 152: 1416–24.
[38] Hu FB, Stampfer MJ, Manson JE *et al*. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. Br Med J 1998; 317: 1341–5.
[39] Kushi LH, Folsom AR, Prineas AS, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 1996; 334: 1156–62.
[40] Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. Am J Clin Nutr 1999; 70 (Suppl): 504S–511S.
[41] Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit and cereal fibre intake and risk of coronary heart disease among men. J Am Med Assoc 1996; 313: 775–9.
[42] Key TJ, Thorogood M, Appleby PN, Burr ML. Dietary habits and mortality in 11 000 vegetarians and health conscious people: results of a 17 year follow up. Br Med J 1996; 313: 775–9.
[43] Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. Int J Epidemiol 1997; 26: 1–13.
[44] Robinson K, Arheart K, Refsum H, Brattstrom T, Boers G *et al*. Low circulating folate and vitamin B_6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary heart disease. Circulation 1998; 97: 437–43.
[45] Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993; 342: 1007–11.
[46] Hertog MGL, Kromhout D, Aravanis C *et al*. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med 1995; 155: 381–6.
[47] Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. Br Med J 1996; 312: 478–81.
[48] Kant AK, Schatzkin A, Graubard BI, Schairer C. A prospective study of diet quality and mortality in women. J Am Med Assoc 2000; 283: 2109–15.
[49] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340: 115–6.
[50] James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr 2000; 71 (Suppl): 343S–348S.
[51] Ridker PM. Evaluating novel cardiovascular risk factors: Can we better predict heart attacks? Ann Intern Med 1999; 130: 933–7.
[52] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836–43.