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Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial

Ram B Singh, Gal Dubnov, Mohammad A Niaz, Saraswati Ghosh, Reema Singh, Shanti S Rastogi, Orly Manor, Daniel Pella, Elliot M Berry

Background The rapid emergence of coronary artery disease (CAD) in south Asian people is not explained by conventional risk factors. In view of cardioprotective effects of a Mediterranean style diet rich in α-linolenic acid, we assessed the benefits of this diet for patients at high risk of CAD.

Methods We did a randomised, single-blind trial in 1000 patients with angina pectoris, myocardial infarction, or surrogate risk factors for CAD. 499 patients were allocated to a diet rich in whole grains, fruits, vegetables, walnuts, and almonds. 501 controls consumed a local diet similar to the step I National Cholesterol Education Program (NCEP) prudent diet.

Findings The intervention group consumed more fruits, vegetables, legumes, walnuts, and almonds than did controls (573 g [SD 127] *vs* 231 g [19] per day p<0·001). The intervention group had an increased intake of whole grains and mustard or soy bean oil. The mean intake of α-linolenic acid was two-fold greater in the intervention group (1·8 g [SD 0·4] *vs* 0·8 g [0·2] per day, p<0·001). Total cardiac end points were significantly fewer in the intervention group than the controls (39 *vs* 76 events, p<0·001). Sudden cardiac deaths were also reduced (6 *vs* 16, p=0·015), as were non-fatal myocardial infarctions (21 *vs* 43, p<0·001). We noted a significant reduction in serum cholesterol concentration and other risk factors in both groups, but especially in the intervention diet group. In the treatment group, patients with pre-existing CAD had significantly greater benefits compared with such patients in the control group.

Interpretation An Indo-Mediterranean diet that is rich in α-linolenic acid might be more effective in primary and secondary prevention of CAD than the conventional step I NCEP prudent diet.

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Introduction

People of south-Asian origin who live in developed countries have an increased mortality rate and susceptibility to coronary artery disease (CAD) compared with indigenous populations.[1–3] The prevalence of CAD is 10% in urban dwellers, but is low in rural dwellers (3–4%) and the lower social classes (1–3%) who consume a diet based on cereal. The risk shows a graded increase in urban dwellers, high social classes, and immigrants, which is linked to pronounced differences in diet and lifestyle.[1,2,4,5] However, the greater susceptibility of people of south-Asian origin to CAD is not explained by conventional risk factors, such as cholesterol and obesity, alone.[2,3] Results from the seven countries study[6] showed that such differences in coronary risk can be explained partly by antioxidants in the diet, variations in physical activity, and smoking. Data from epidemiological and cohort studies[7,8] also showed that increased consumption of fruits, vegetables and legumes, grains, nuts, and n-3 fatty acids might be associated with a decreased risk of CAD, and deaths attributable to coronary disease. Results from randomised controlled intervention trials[9–14] suggest that treatment with n-3 fatty acids and antioxidant rich foods such as fish, fruits, vegetables, legumes, and nuts can reduce cardiac events and related mortality in patients with CAD. Evidence suggests that dietary patterns could well have an effect on the mechanisms of atherosclerotic plaque vulnerability and the progression of thrombosis.[15–17]

The scientific advisory committee of the American Heart Association (AHA) has stated that a Mediterranean-style diet has impressive effects on the progression of cardiovascular disease.[13] Significant findings from the Lyon Heart Study[9,10] and other such studies,[11,12] have prompted an aggressive pursuit of the benefits of such dietary modifications in other regions of the world.[11,12,15] If the Lyon diet is also of benefit in non-Mediterranean populations, such as south-Asians, it might provide an economically feasible and realistic method to reduce CAD in these regions. The AHA statement[13] raised some issues for investigators: geographical and non-measured cultural and social differences in potential target populations; enhanced definition of baseline diets of both trial groups at the beginning of the study; enhanced and continuing analysis of true dietary patterns throughout studies; and an assessment of any changes in combined risk factors during the study. We have addressed some of these issues here. In patients with clinical CAD or with recognised risk factors, we assessed the effect of an Indo-Mediterranean diet consisting of whole grains including legumes, fruits, vegetables, nuts, and mustard or soybean oil.

Methods

Participants

We recruited participants through advertisements in newspapers and local service clubs that invited people older than 25 years with hypercholesterolaemia, hypertension,

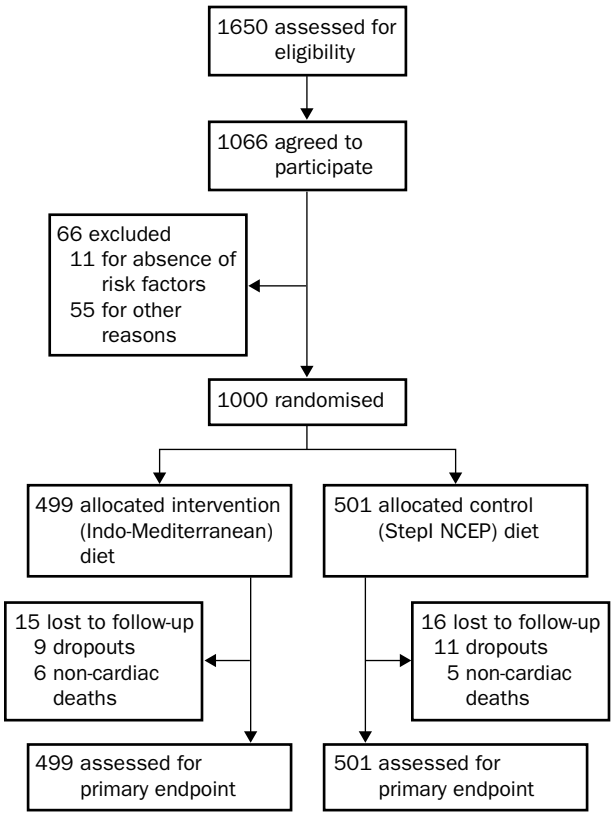


Figure 1: **Trial profile**

diabetes mellitus, or heart attack for free medical advice about diagnosis and treatment of their disorders. Patients were enrolled by a dietician and a physician. The diagnostic criteria for these cardiovascular risk factors were those standardised by WHO.[18] There were between 50 and 150 respondents at each centre. Most respondents were from social class 1–3 (including shopkeepers, office workers, businessmen, teachers, doctors, engineers, and artisans) and had sedentary occupations.[3–5] The recruitment criterion was one or more of the major risk factors for CAD,[18,19] (hypertension, hypercholesterolaemia, or diabetes mellitus (418)), or angina pectoris (105) or a previous myocardial infarction (478) in absence or presence of other risk factors. Of 1650 people who responded to advertisements from 17 centres over 4 years, 1066 between ages 28 and 75 years, volunteered to participate in the trial (figure 1).

For patients without a documented history, we used exercise electrocardiography after either bicycle ergometry (446) or treadmill tests (76) to detect CAD. For the other patients (478), a previous record of diagnosis and treatment of myocardial infarction was available. We excluded patients because of: absence of major risk factors (11), cancer (7), chronic diarrhoea or dysentery (8), a blood urea of more than 6·6 mmol/L (8), arthritis (5), dislike of the intervention diet (12), refusal of laboratory testing, (9) and death before randomisation (6). The ethics committee at the Medical Hospital and Research Centre at Moradabad approved the study, and we obtained written informed consent from all participants.

We classified patients who had a body-mass index (BMI) between 25 and 29·9 kg/m^2 as overweight, and obesity was defined as a BMI of 30 kg/m^2 or greater. We defined weight loss as a reduction of 0·5 kg or greater. Patients who completed less than 3 km of walking per day during occupational, household, or leisure time activities were defined as physically inactive. Hypertension was diagnosed if blood pressure was greater than 140 mm Hg systolic or 90 mm Hg diastolic. Diabetes mellitus was diagnosed when fasting blood glucose concentrations were greater than 7·7 mmol/L, and postprandial concentrations were greater than 11·1 mmol/L, 2 h after ingestion of 75 g of glucose. Alternatively, patients were classified as having hypertension, or diabetes if a documented history of their diagnosis and treatment was available. Hypercholesterolaemia was determined by a serum cholesterol greater than 5·2 mmol/L, with confirmation by a second estimation. All patients with angina pectoris and myocardial infarction had treatment for between 10 days and 1 year, and a documented history of diagnosis and treatment in accordance with criteria specified by WHO.[18]

Procedures

We met with participants every week, for 3 weeks. To establish baseline dietary intake, we asked patients to maintain their usual lifestyle, and to record their daily diet and drug intake. Patients were required to provide the weight of fruit, vegetables, and nuts consumed. Information from the diaries was cross-checked by dieticians who questioned patients about household measures, food models, and food portions to find the exact quantity of food consumed. Baseline clinical, electrocardiographic, radiological, and laboratory data were obtained from participants during the 3-week observation. Every patient was then individually assessed by the dietician and a physician who made a final decision about eligibility for the trial. Participants were then stratified to have a balance of patient characteristics in each intervention arm. These characteristics included serum total cholesterol greater than 5·2 mmol/L, age older than 50 years, and history of myocardial infarction or angina pectoris. Patients were assigned to either the intervention or control group, by selection of a card from a pile of equal numbers of cards for each group. The intervention group consisted of 499 patients, and the control group 501. Hypolipidaemic drug treatment was prescribed at the discretion of the treating physician.

In both groups, two-thirds of patients were vegetarian. The remaining third ate two to five eggs, and one to two portions of meat a week. All participants consumed milk, butter, clarified butter (Indian ghee), and trans fatty acids (vegetable ghee made from partly hydrogenated oils). Vegetarian participants consumed more milk, vegetable ghee, peanut oil, and clarified butter than did non-vegetarians.[20] Participants in both groups were advised to eat food substitutes that would provide a dietary intake similar to that recommended by the National Cholesterol Education Program (NCEP)[21] in the step I prudent diet. This diet recommends that less than 30% of energy comes from total fat, less than 10% from saturated fat, and that less than 300 mg of cholesterol is consumed per day. Additionally, patients in the intervention group were advised to consume at least 400–500 g of fruits, vegetables, and nuts per day, (ie, 250–300 g of fruit, 125–150 g of vegetables, and 25–50 g of walnuts or almonds). This group was also encouraged to eat 400–500 g of whole grains, legumes, rice, maize, and wheat) daily, as well as mustard seed or soy bean oil, in three to four servings per day, which is consistent with recommendations from the Indian Consensus Group.[19] The aim of these dietary recommendations was to provide people in the intervention group with plenty of phytochemicals, antioxidants, and α-linolenic acid (the major n-3 fatty acid in these foods). Such recommendations are also made by WHO[22] and the Indian Consensus Group[19] to prevent chronic diseases.

Patients from both groups were also advised to walk briskly for a minimum of 3–4 km, or to jog intermittently for a minimum of 10–15 minutes per day. All participants with CAD were instructed to take sublingual nitroglycerine and cease exercising in the event of chest pain, substantial sweating, weakness, or dyspnoea. Smoking and alcohol consumption were discouraged, and we encouraged mental relaxation through yoga meditation techniques and breathing exercises in both groups. Appropriate drugs for angina pectoris, arrhythmias, raised blood pressure, diabetes, and other complications were provided to both groups.

Data collection and follow up

We calculated 24-h nutrient intakes for all patients with Indian food-composition tables[21] and patients' weekly diet diaries. All participants were asked to complete for 1 week a record of food intake, and to record occupational, household, and leisure time physical activity for weeks 1–4, then at weeks 4, 8, 12, and 24, then at 12 week intervals, to assess dietary adherence and exercise activity.[23] In both groups, completed diaries were checked by the dietician on every visit with the help of a questionnaire that used household measures and food models, to estimate caloric value of food portions and to reinforce dietary adherence. Control patients were given an information sheet on the step I prudent diet at each visit, intervention group patients were given a thorough explanation of the usefulness of the experimental diet, and the types of food that are rich in n-3 fatty-acids. At all meetings, dieticians provided additional motivation to both groups to adhere to the advice about diet and exercise.

Patients with diabetes mellitus, angina pectoris, a history of myocardial infarction, or hypertension who visited the physician frequently, received more frequent dietary advice during the 2 years of follow up than those who did not. At every visit, bodyweight, tobacco use, and alcohol consumption were recorded by the dietician with a questionnaire, which was identical for both groups.

In both groups, clinical data, drug intake, adverse events, coronary events, hospital admission, blood pressure, blood glucose, and blood lipids were recorded by a physician unaware of patient diet. A 12-lead electrocardiograph was done every 3 months for patients with CAD and for people with any symptoms or signs suggestive of cardiac arrhythmias, heart enlargement, ischaemia, or infarction. Routine annual electrocardiography was done for all other participants. Patients recorded symptoms of angina pectoris in a diary. Chronic left ventricular failure, ventricular hypertrophy, dysrhythmias, and positive exercise tests were diagnosed in accordance with standard criteria, including those of the New York Heart Association (NYHA class II–IV).

Cardiovascular events

The principal endpoints of the study were fatal or non-fatal myocardial infarctions, sudden cardiac deaths, and the combined total of these events.[18] Other important events, such as the need for coronary angiography, angioplasty, or bypass surgery were also recorded by a cardiologist, from whom the dietary regimens were concealed.

Fatal myocardial infarction was diagnosed when a hospital record was consistent with cause of death, and there was either preterminal hospital admission with a definite myocardial infarction, or a record in which myocardial infarction had been noted. We classified sudden cardiac death when coronary heart disease had been noted, and death occurred within 1 h of onset of symptoms. A death certificate in which background CAD had been noted, but not evidence that was suggestive of a cardiac death, was classified as a suspected cardiac death. Non-fatal myocardial infarction in inpatients was diagnosed if a diagnostic electrocardiograph had been done at the time of the event; or if the patient had had ischaemic cardiac pain and diagnostic enzyme measurements (creatine kinase, lactate dehydrogenase, or serum glutamic oxalotransferase of at least twice the higher limit of normal), or had had ischaemic cardiac pain and equivocal enzyme measurement and an equivocal electrocardiograph. The diagnosis of myocardial infarction was also considered in patients who had not been admitted if they had chest pain, breathlessness, or syncope, with a diagnostic electrocardiograph at the time of event, or new electrocardiographic changes consistent with myocardial infarction at routine check-up. A cardiologist who did not have clinical information about the dietary regimens did the electrocardiographic coding and analysis.[21] Possible myocardial infarction was suspected in the presence of ischaemic cardiac pain and equivocal enzyme concentrations, or of an unclear electrocardiograph. Such events were not included in the total cardiac events as primary endpoints.

Laboratory data

Laboratory data were obtained from all participants during the 3-week-long observation, and at 12 and 24 weeks, and after 2 years of follow-up. We measured concentrations of glucose, total cholesterol, HDL and LDL cholesterol,[24] and triglycerides,[25] and did complete blood counts. Total

	Intervention diet (n=499)	Control diet (n=501)
Patients' characteristics		
Age (years)	49 (10)	48 (9)
Body weight (kg)	66 (7·5)	66(7·3)
Body mass index (kg/m²)	24·3 (3·0)	24·1 (2·3)
Systolic blood pressure (mm Hg)	132 (17)	131 (17)
Diastolic blood pressure (mm Hg)	86 (10)	86 (9)
Frequency of risk factors		
Male	454 (91%)	443 (88%)
Hypercholesterolaemia	357 (72%)	368 (74%)
Hypertension	194 (39%)	173 (35%)
Diabetes mellitus	93 (19%)	117 (23%)
Smoking		
1–15 cigarettes daily	102 (20%)	79 (16%)
>15 cigarettes daily	152 (31%)	140 (28%)
Ex-smokers	40 (8%)	32 (6%)
Overweight	115 (23%)	111 (22%)
Obesity	24 (5%)	22 (4%)
Drug therapy received		
Aspirin	268 (54%)	275 (55%)
Nitrates	202 (41%)	190 (38%)
Verapamil	75 (15%)	82 (16%)
Lovastatin	36 (7%)	31 (6%)
Furosemide	32 (6%)	30 (6%)
Disopyramide	28 (6%)	32 (6%)
Fibrates	20 (4%)	22 (4%)
Coronary artery disease	290 (58%)	293 (59%)
Post myocardial infarction	235 (47%)	243 (49%)
Recent myocardial infarction (<4 weeks)	177 (36%)	170 (34%)
Angina pectoris	55 (11%)	50 (10%)
Exercise test positive	242 (49%)	255 (51%)
Left ventricular hypertrophy	38 (8%)	31 (6%)
NYHA class II–IV	23 (5%)	20 (4%)
Ventricular ectopics		
>8 per min	51 (10%)	45 (9%)
3 consecutively	11 (2%)	13 (3%)
Stroke	2 (0·4%)	2 (0·4%)
Others	2 (0·4%)	2 (0·4%)

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics**

	Intervention diet (n=499)			Control diet (n=501)			Corrected difference†	p value at 2 years
	Baseline	2 years	Mean change*	Baseline	2 years	Mean change		
Total energy (kCal)	2159 (166)	2015 (141)	–144	2170 (162)	2089 (135)	–81, p<0·0001	–63	<0·0001
% CHO	57·0 (1·8)	59·5 (1·7)	+2·5	56·9 (1·8)	56·0 (1·3)	–0·9, p<0·0001	+3·4	<0·0001
% Complex CHO	41·2 (2·1)	48·1 (1·5)	+6·9	39·5 (1·7)	38·7 (1·3)	–0·7, p<0·0001	+7·6	<0·0001
Total fibre, g/day	25·0 (2·2)	48·1 (1·5)	+23·1	25·9 (1·4)	25·9 (1·1)	0, p=0·4	+23·1	<0·0001
Soluble fibre, g/day	13 (1)	25 (1)	+12	13·7 (1·0)	13·6 (0·5)	–0·1, p=0·0524	+12·1	<0·0001
% Protein	14·8 (1·4)	14·2 (0·9)	–0·6	14·6 (1·1)	14·9 (0·8)	+0·3, p<0·0001	–0·9	<0·0001
% Fat	27·8 (2·1)	26·3 (2·0)	–1·5	28·0 (1·8)	29·1 (1·6)	+1·1, p<0·0001	–2·6	<0·0001
% Saturated	13·0 (1·6)	8·2 (1·9)	–4·8	12·5 (1·3)	12·1 (1·6)	–0·4, p=0·0002	–4·4	<0·0001
% PUFA	7·5 (1)	8·1 (0·8)	+0·6	7·4 (0·8)	7·4 (0·8)	0, p=0·43	+0·6	<0·0001
% MUFA	7·3 (1·6)	10·0 (1·6)	+2·7	8·1 (1·7)	9·6 (1·3)	+1·5, p<0·00001	+1·3	<0·0001
P/S ratio	0·58 (0·07)	1·03 (0·22)	+0·45	0·60 (0·07)	0·61 (0·04)	+0·01, p<0·0001	+0·44	<0·0001
n-3 fatty acids	0·46 (0·20)	1·79 (0·36)	+1·33	0·53 (0·19)	0·78 (0·16)	+0·25, p<0·0001	+1·07	<0·0001
Cholesterol (mg/day)	209 (22)	125 (39)	–84	207 (20)	207 (22)	0, p=0·71	–84	<0·0001
Salt (g/day)	9·0 (1)	8·4 (1)	–0·6	9·0 (1·0)	9·5 (1·1)	+0·5, p<0·0001	–1·1	<0·0001
FVL (g/day)	215 (29)	573 (127)	+358	207 (23)	231 (19)	+24, p<0·0001	+334	<0·0001
Grains (g/day)‡	120 (21)	252 (75)	+132	127 (25)	132 (31)	+5, p<0·0001	+127	<0·0001
Oil (g/day)§	10·0 (3·5)	31 (6·5)	+21	12·4(4·1)	15·2 (5·5)	+2·8, p<0·0001	+18·2	<0·0001

PUFA=polyunsaturated fatty acids. MUFA=monounsaturated fatty acids. P/S=polyunsaturated to saturated fat ratio. FVL=fruits, vegetables, nuts, and legumes. Data presented as mean (SD). *Mean difference of baseline to 2-year value changes between groups, intervention diet minus control diet. †p<0·0001 for all changes. ‡Whole grains (rice, maize, wheat). §Mustard and/or soybean oils.

Table 2: **Nutrient indices at entry to study and after 2 years**

cholesterol concentration was measured directly in serum by enzymatic methods, and HDL cholesterol was measured after precipitation of VLDL and LDL cholesterol. In patients with high cholesterol at entry, tests were repeated for confirmation.

Statistical analysis

We calculated sample size on the basis of a difference between the two groups in the total number of cardiac events, assuming a 14% risk in the control group, an 8% risk in the intervention group, a power of 85%, and a two-tailed test with α=0·05. We estimated the risks in groups on the basis of previous data,[11] and expected a reduced rate of events because of preventive measures taken in both control and intervention groups.

Data were analysed by intention to treat. We did baseline comparisons using a *t* test for continuous variables and a χ^2 test for binary variables. Comparison of risk factors and nutrient intakes after 2 years were done by a test based on the values at the end of follow-up, as well as a *t* test based on differences from baseline. These differences were assessed twice: first, we included all patients and used the last available records of patients who were lost to follow-up, and, second, we did an analysis which omitted patients lost to follow-up. Results of the two analyses did not differ, and data are therefore shown for the analysis that includes all patients. Event-free survival for each endpoint and the composite outcome of all cardiac events were estimated by the Kaplan-Meier method. We estimated rate ratios with Cox's proportional-hazards model, after adjustment for age, sex, BMI, blood pressure, and cholesterol at baseline. Two-tailed p values less than 0·05 were judged significant.

Results

Participants (n=1000) were randomly assigned to the intervention diet (499) or control diet (501). Because patients were stratified by risk factor or presence of CAD, both groups were comparable for over 30 characteristics, including complications (table 1). Hypertension was a common risk factor in both groups. Hypercholesterolaemia was much the same in the two groups, and for most patients serum cholesterol was between 5·2–6·7 mmol/L. In both groups, roughly half the patients were smokers at entry to the study. Frequencies of therapeutic drug use were closely similar in both groups. The proportions of patients with a sedentary lifestyle were almost identical at baseline in both groups (450 [90%] *vs* 462 [90%]) for intervention and control groups, respectively). All patients with diabetes mellitus received either glybenclamide or glipizide. More than half the patients in each group had CAD at baseline, defined as angina pectoris or a past myocardial infarction. A third of participants in both groups had had a myocardial infarction within the previous 4 weeks. Other complications of CAD with a poor long-term prognosis were slightly more common in the intervention group than in controls.

Because follow-up appointments were close to the participants' homes, and because Indians prefer non-

	Intervention diet (n=499)			Control diet (n=501)			Corrected difference*†	p value at 2 years between groups
	Baseline	2 years	Mean change*†	Baseline	2 years	Mean change		
Weight (kg)	66 (7·5)	62 (6·1)	–4	66 (7·3)	65 (6·6)	–1, p<0·0001	–3	<0·0001
Body-mass index (kg/m^2)	24·3 (3·0)	23·0 (2·6)	–1·3	24·1 (2·3)	23·8 (2·2)	–0·3, p<0·0001	–1·0	<0·0001
WHR (cm)	91 (2)	90 (3)	–1	90 (4)	91 (3)	+1, p=0·0215	–2	<0·0001
Systolic blood pressure (mm Hg)	132 (17)	127 (16)	–5	131 (17)	129 (15)	–2, p<0·0001	–3	<0·0001
Diastolic blood pressure (mm Hg)	86 (10)	83 (9)	–3	86 (9)	85 (8)	–1, p<0·0001	–2	<0·0001
Cigarettes per day	19·1 (8·1)	15·6 (6·3)	–3·5	17·3 (7·3)	12·5 (5·4)	–4·8, p<0·0001	+1·3	<0·0001
Total cholesterol (mmol/L)	5·74 (0·98)	5·04 (0·91)	–0·70	5·77 (0·98)	5·59 (1·03)	–0·18, p<0·0001	–0·52	<0·0001
LDL (mmol/L)	3·64 (0·78)	3·0 (0·62)	–0·64	3·54 (0·67)	3·39 (0·70)	–0·15, p<0·0001	–0·49	<0·0001
HDL (mmol/L)	1·16 (0·26)	1·19 (0·21)	+0·03	1·14 (0·15)	1·11 (0·21)	–0·03, p=0·0288	+0·06	<0·0001
Triglycerides (mmol/L)	1·84 (0·38)	1·48 (0·35)	–0·36	1·85 (0·28)	1·74 (0·30)	–0·11, p<0·0001	–0·25	<0·0001
FBG (mmol/L)	5·99 (1·39)	5·55 (1·22)	–0·44	5·94 (1·55)	5·77 (1·39)	–0·17, p<0·0001	–0·27	<0·0001

WHR=waist to hip circumference ratio; FBG=fasting blood glucose. Data presented as means (SD). *Mean difference of baseline to 2-year value changes between groups, intervention diet minus control diet. †p<0·0001 for all changes.

Table 3: **Cardiovascular risk factors at baseline and after 2 years**

	Intervention diet (n=999)	Control diet (n=501)	Unadjusted rate ratios (95% CI)	Adjusted rate ratios (95% CI)
Person weeks at risk	49 238	46 554		
Non fatal MI	21 (4·2%)	43 (8·6%)	0·49 (0·29–0·81)	0·47 (0·28–0·79)
Fatal MI	12 (2·4%)	17 (3·4%)	0·69 (0·33–1·45)	0·67 (0·31–1·42)
Sudden cardiac death	6 (1·2%)	16 (3·2%)	0·37 (0·14–0·94)	0·33 (0·13–0·86)
Total cardiac endpoints	39 (7·8%)	76 (15·2%)	0·50 (0·34–0·73)	0·48 (0·33–0·71)

MI=myocardial infarction. Adjustment made for baseline age, gender, body-mass index, cholesterol and blood pressure.

Table 4: **Numbers and rate ratios for separate and combined cardiac endpoints**

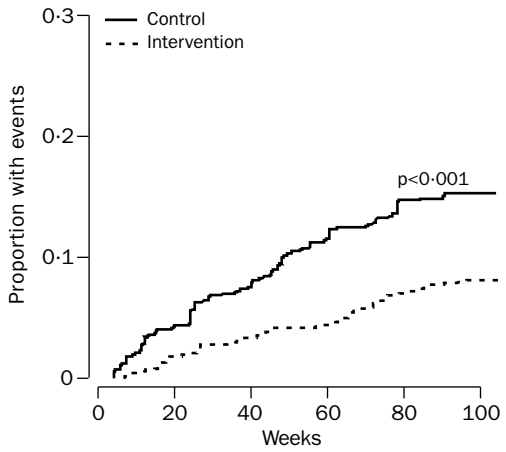
pharmacological treatment and vegetarian diets, drop-out rates were low. After 2 years follow-up, there were nine dropouts in the intervention group and 11 in the control group, all of which happened after 12 weeks of follow-up. Apart from these dropouts, 115 patients in the intervention group and 100 in the control group missed their regular follow-up visits, although they were following the intervention programme. Dropouts from the intervention group showed a decrease in plasma lipoproteins and bodyweight after 12 weeks of follow-up, suggesting that they were adhering to the diet and lifestyle changes that we recommended (data not shown). Dietary intake of fruit, vegetables, legumes, and oils increased in both groups but much more so in the intervention group, suggesting that participants adhered to the recommended diets (table 2).

Lifestyle characteristics, such as number of meals or snacks consumed per day, number of hours sleep per night, duration of brisk walks or jogs, and time spent doing mental relaxation did not differ significantly between the groups (data not shown).

Baseline nutrient intakes showed no biologically important differences in the consumption of carbohydrates, fatty acids, and cholesterol between the two groups (table 2). At the end of the 2-year follow-up, n-3 fatty acid intake was slightly higher in the controls than in those on the intervention diet. Intake of dietary fibre, salt, fruit, vegetable, nut, and whole grains between the groups was much the same at baseline, but after 2 years, patients on the intervention diet consumed a greater percentage of calories from total and complex carbohydrates, had a higher polyunsaturated to saturated fat ratio, and lower energy, total fat, saturated fat, and cholesterol than had controls. α-linolenic acid intake was significantly greater in the intervention group than in controls. Total fruit, vegetable, nuts, and whole grain intakes and mustard and soy bean oil consumption were also significantly higher in the intervention group.

After 2 years, both groups had a significant decrease in total cholesterol and LDL cholesterol, and triglycerides—the effect being larger in the intervention group than in the controls (table 3). HDL cholesterol rose in the intervention group, but fell in controls. Fasting blood glucose, BMI, and blood pressures were significantly reduced in those on the intervention diet compared with controls. The reduction in smoking in the two groups was significant.

At 2 years of follow-up, the intervention group, compared with control group showed a significant reduction in the proportion of patients taking nitrates (101 [21%] *vs* 152 [31%] p=0·0001), verapamil (37 [8%] *vs* 68 [14%], p=0·001), and disopyramide (8 [2%] *vs* 29 [6%], p<0·0001). At the end of the trial, participants in both groups had become less sedentary, and scores for mental relaxation showed no significant difference between groups.



Numbers at risk

Intervention group	499	490	482	471	456	450
Control group	501	478	457	437	414	419

Figure 2: **Kaplan-Meier cumulative event curves**
Proportion of patients with fatal myocardial infarction, non-fatal myocardial infarction, or sudden cardiac death.

The intervention group had a significant reduction in risk of non-fatal myocardial infarction, sudden cardiac death, and total cardiac endpoints compared with the controls (table 4). There were also fewer, but not significantly fewer, fatal myocardial infarctions. Suspected cardiac deaths (two in the intervention group, one in the controls) were not included in the analysis, although their inclusion in the total cardiac end points did not change the results significantly (data not shown). Kaplan-Meier analysis of curve for event-free survival for total cardiac endpoints suggests a highly beneficial effect of the intervention diet (figure 2). With the Cox's proportional-hazards model, rates for cardiac events were estimated for the intervention group relative to the controls, after we had adjusted for age, sex, BMI, cholesterol, and blood pressure at baseline (table 4). Only one event occurred per person.

Cardiac complications such as angina pectoris, post-exercise electrocardiographic changes, left ventricular strain (ST and T segment depression on V5 and V6 leads of electrocardiograph), left ventricular hypertrophy, and arrhythmias requiring treatment were significantly less common in the intervention group than in controls (table 5).

	Intervention diet (n=499)	Control diet (n=501)	p
Angina pectoris	33 (7%)	55 (11%)	0·0133
Positive Exercise test	81 (16%)	178 (36%)	<0·0001
LV strain	45 (9%)	80 (16%)	0·0008
LV hypertrophy	25 (5%)	55 (11%)	0·0004
NYHA III, IV	7 (1·4%)	9 (1·8%)	0.61
Heart Failure	11 (2·2%)	35 (7%)	0·0003
Ectopics 8/min	8 (1·6%)	30 (6%)	0·0003
2 in a row	3 (0·6%)	5 (1·0%)	0·47
Stroke	7 (1·4%)	13 (2·6%)	0·17
CABG or angioplasty	6 (1·2%)	16 (3·2%)	0·0304
Suspected cardiac death	2 (0·4%)	1 (0·2%)	0·56
Stroke death	2 (0·4%)	3 (0·6%)	0·65
Total cardiovascular events	49 (10%)	96 (19%)	<0·0001
Gall stones	4 (0·8%)	5 (1·0%)	0·73
Accidents	4 (0·8%)	3 (0·6%)	0·71
Cancer	2 (0·4%)	2 (0·4%)	1·00
Accident deaths	1 (0·3%)	0	0·32
Cancer deaths	1 (0·3%)	1 (0·2%)	1·00
Total deaths	24 (5%)	38 (8%)	0·0640

LV=left ventricular; NYHA=New York Heart Association; CABG=coronary artery bypass grafting. Data are number (%).

Table 5: **Cardiac complications and non-cardiac morbidity and mortality**

Pre-existing coronary artery disease (angina pectoris and myocardial infarction), hypertension, or hypercholesterolaemia at baseline did not determine the effect of the intervention. We have tested interactions with respect to all these risk factors and none was significant (data not shown).

Discussion

Our results show that consumption of an Indo-Mediterranean diet rich in α-linolenic acid was associated with a significant reduction in non-fatal myocardial infarction, sudden cardiac death, and total cardiac endpoints. Additionally, the intervention diet showed improvements in the number of surrogate traditional risk factors, which were better than those seen in controls who adhered to the prudent step I diet.

The intervention diet was based on that suggested by the scientific advisory committee of the AHA,[13] WHO, and other studies.[9,10,12,22,26] The Indo-Mediterranean Diet Heart Study has shown that many lacto-vegetarian and sedentary patients with major cardiac risk factors, and those with CAD, can be motivated to make comprehensive dietary and lifestyle changes over at least 2 years. Our intervention programme seems to be a safe adjunct to the prudent diet, and is compatible with other treatments given simultaneously, such as physical activity and medications.

The prevalence of CAD is low in rural dwelling Indians, when compared with urban dwellers and immigrant Indians (3%, 10%, 14%, respectively).[1-3] Rural populations at low risk consume 300–500 g per day of whole grains, such as wheat, rice, millet, and pulses, and mustard oil as visible fat (rich in n-3 fatty acids).[1-5] However, urban dwellers and immigrants substitute potato and refined carbohydrates for grains, and use proatherogenic vegetable ghee and clarified butter in place of oils. The increased susceptibility of south Asians to CAD is not explained only by serum cholesterol, hypertension, sedentary lifestyle, or smoking. Indian studies[1,4,21] show inadequate fruit and vegetable consumption. The consequent deficiency in the antioxidant vitamins A and C allows overproduction of free radicals,[7,26,27] which might be worse in people who consume a diet high in polyunsaturated fat (including n-3 fatty acid), in smokers, or in those who eat a lot of Indian ghee[28] (cholesterol oxide), thus increasing the risk of CAD in several ways.

Platelet adhesion, which is important in thrombosis, is likely to occur when antioxidant and n-3 fatty acid status is low. Arterial endothelium, myocardium, and pancreatic β-cells are all protected against free radical damage by a combination of dietary n-3 fatty acids and antioxidants.[27] Oxidised blood lipids are proinflammatory and, in the presence of low n-3 fatty acids, might also increase thrombosis. Increased consumption of fruits, vegetables, legumes, and nuts, rich sources of n-3 fatty acids, antioxidant vitamins, flavonoids, and polyphenols, could be beneficial through some of these mechanisms.

Results from the Lyon Diet Heart study[9,10] showed that increased consumption of fruits, vegetables, nuts, and n-3 fatty acid-rich margarine was associated with an almost 70% reduction in coronary events and cardiac deaths without a decrease in serum cholesterol, triglycerides, or an increase in HDL cholesterol. Results of the Indian Experiment on Infarct Survival study[11] showed a significant fall in the number of cardiac events and deaths after increased intake of fruits and vegetables in patients who had had a recent myocardial infarction. However, results of many early trials of diet for secondary prevention of CAD failed to show any benefits.[29,30]

Since most recent intervention trials[31,32] of antioxidant vitamin supplements in the prevention of CAD have shown little or no benefit, other phytochemicals present in whole grains, fruits, vegetables, nuts, and oils might interact with vitamins in the prevention of CAD. These were the conclusions of the Indian Experiment of Infarct Survival.[33] Support for this view comes from results of long-term follow-up studies.[6,7] Results of an intervention trial in 120 000 people, showed that daily consumption of fresh fruit and vegetables was protective against coronary heart disease.[7]

The AHA expert panel[13] has raised important issues about baseline dietary intakes and sociocultural factors of target populations, some of which we have addressed to confirm the applicability of the Mediterranean diet in the prevention of CAD in a geographically different population. Investigators in the Lyon study and a previous Indian experiment did not emphasise the consumption of whole grains, although the diets did include such measures.[9-12] The NCEP step I and II diets are characterised by low amounts of total and saturated fats, and cholesterol, and a high intake of fruits, vegetables, and whole grain products. These diets have been widely recommended for treatment of CAD.[20]

Our study targeted populations that have yet to learn the messages for prevention of heart disease. Baseline diets in our participants contained large amounts of total and saturated fats, cholesterol, and refined carbohydrates in the form of excess milk, clarified butter, butter, cream, eggs, sugar, refined bread and small amounts of whole grain products, compared with low-risk rural populations. Dietary supplementation with wheat, rice, maize, legumes, fruits, vegetables, and nuts was associated with a decrease in cardiovascular risk factors in the intervention group. Substantial enhancement of the effectiveness of dietary recommendations[20] might be provided by integrating features of our study diet and the Lyon Diet Heart Study.

Several methodological issues in our study should be addressed. Participant adherence to diet and lifestyle advice is a major difficulty. Patients might not eat and do as they are advised, and they might have learnt to complete weekly diaries in accordance with the perceived wishes of the dietician. Thus, assessment of nutrient intakes through diaries and questionnaires is open to bias. However, in our study, weekly diet diaries were cross-checked by the dietician's questionnaire. Participants were heterogeneous with respect to risk factors for CAD, which might be regarded as a weakness. However, we believe that this feature might indeed be a strength, because the population would be representative of patients typically encountered in practice. A similar study population was also used in the HOPE study.[32]

The benefits noted in our study were also present in patients with pre-existing CAD, indicating that the diet was an important help in secondary prevention. The duration of intervention and the sample size would have to be larger than those in our study to draw definite conclusions about the effect of the intervention on non-cardiac and total mortality.

Although multiple interventions that aim to reduce CAD might be criticised for being methodologically weak (because assessment of the effect of each one separately is difficult), the potential benefits of this approach justifies its evaluation as a way to decrease CAD incidence and mortality. Further analyses of our data are being done to determine the relative contributions of different antioxidant vitamins, flavonoids, and polyunsaturated fatty acids[34] to the incidence and total mortality attributable to CAD.[35] However, our study provides important lessons about diet and cardiovascular disease. First, CAD is seen in Asia despite an absence of conventional risk factors, and despite the consumption of a low fat (<30% energy) diet. Second, Asian populations are mainly vegetarian and do not have a

high prevalence of obesity or insulin resistance syndrome. Therefore, dietary interventions might be considered of little benefit in the treatment of CAD. Third, we have shown that a diet rich in fruit, vegetables, legumes, with a high α-linolenic acid content is associated with a decrease in cardiovascular events. Fourth, n-3 fatty acids consumed as mustard or soy bean oils, walnuts, whole grains, and leafy vegetables, rather than as fish or fish oil supplements, might also reduce the cardiovascular disease risk in populations that already consume a prudent, low fat diet. Fifth, the Indo-Mediterranean diet is a safe and economical way to improve the health of poor populations because the whole grains, fruits, vegetables, and oils used in this study were seasonal, traditional, and produced by farmers at a cost of about US$1 per day. Last, our trial in a non-Western population has shown that, over 2 years, a diet enriched with fruit, vegetables, nuts, whole grains, and mustard or soy bean oil is associated with a pronounced decline in CAD morbidity and mortality, without an increase in non-cardiac deaths, and in the presence of improved metabolic profiles. The long-term benefits may be even more substantial.

Contributors

R B Singh coordinated the study. G Dubnov did data entry, statistical analysis, and interpretation. M A Niaz analysed blood, recruited patients, and did data collection. S Ghosh and R Singh recruited patients and collected data. S S Rastogi designed the study, recruited patients, and did data collection. O Manor did statistical analysis. D Pella interpreted data. E M Berry did statistical analysis and data interpretation. R B Singh, G Dubnov, and E M Berry wrote the manuscript.

Conflict of interest statement

None declared.

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