

THE LANCET

Vol 337

Saturday 5 January 1991

No 8732

ORIGINAL ARTICLES

Risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene

R. A. RIEMERSMA D. A. WOOD C. C. A. MACINTYRE
R. A. ELTON K. F. GEY M. F. OLIVER

The relation between risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene was examined in a population case-control study of 110 cases of angina, identified by the Chest Pain Questionnaire, and 394 controls selected from a sample of 6000 men aged 35-54. Plasma concentrations of vitamins C and E and carotene were significantly inversely related to the risk of angina. There was no significant relation with vitamin A. Smoking was a confounding factor. The inverse relation between angina and low plasma carotene disappeared and that with plasma vitamin C was substantially reduced after adjustment for smoking. Vitamin E remained independently and inversely related to the risk of angina after adjustment for age, smoking habit, blood pressure, lipids, and relative weight. The adjusted odds ratio for angina between the lowest and highest quintiles of vitamin E concentrations was 2.68 (95% confidence interval 1.07-6.70; $p=0.02$). These findings suggest that some populations with a high incidence of coronary heart disease may benefit from eating diets rich in natural antioxidants, particularly vitamin E.

Lancet 1991; 337: 1-5.

Introduction

There is growing interest in the possible role of free radicals in the development of atheroma. Oxidative modification of low density lipoprotein (LDL) particles in the arterial subendothelium results in structural changes, which are postulated to make them more atherogenic than native LDL.¹ The most readily available naturally occurring antioxidants in food are vitamins E and C. Vitamin E is the major antioxidant in the lipid phase and protects polyunsaturated fatty acids from peroxidation. Vitamin C acts in the water-soluble compartment and has a sparing effect on vitamin E.

We have tested the hypothesis that plasma concentrations of vitamins with antioxidant properties may be related to the risk of angina and have measured the extent to which such risk is independent of classic risk factors for coronary heart disease (CHD).

Subjects and methods

The design of this case-control study has been described elsewhere.² Briefly, the population sampled was men aged 35-54 years listed on the Lothian Health Board Central Register with an address in the city of Edinburgh. A systematic sample of 6000 men was drawn from the register and surveyed by postal questionnaire, which included a self-administered version of the World Health Organisation Chest Pain Questionnaire.³ We have previously documented dietary changes in subjects who had been told that they had CHD.⁴ To avoid the confounding effect of such dietary changes we included only subjects who answered positively to the chest pain questionnaire, but who had never seen a doctor on account of these symptoms. These angina cases were compared with controls matched for age and sex drawn from the same population, who gave negative replies to the chest pain questionnaire and also had no reported history of CHD.

125 cases of angina pectoris found in the survey (response rate 83%) and 430 healthy controls (response rate 76%) attended for medical assessment between April, 1983, and April, 1984. Complete vitamin data were obtained for 110 cases of angina and 394 controls. A self-administered questionnaire recorded demographic information, medical history, smoking habit, alcohol intake, and diet. Height, weight ('Seca' weighing scales model 760), and supine blood pressure (two recordings; Hawksley random zero sphygmomanometer) were measured by one observer. A blood sample was taken from the antecubital fossa without a tourniquet for measurement of non-fasting plasma lipids, vitamins, and platelet fatty acid composition, and the samples were processed immediately in the clinic. Adipose tissue was sampled under local anaesthetic from the anterior abdominal wall.

10 ml heparinised blood for analysis of plasma vitamins was centrifuged immediately at 2000 *g* for 10 min at room temperature. 0.5 ml plasma was mixed with 4.5 ml washed metaphosphoric acid for the analysis of vitamin C, and the remaining plasma was frozen at -40°C in 1 ml volumes in Eppendorf tubes. Vitamin C was analysed fluorimetrically by means of iodine oxidation followed by condensation with 1,2-phenylenediamine;⁵ the coefficient of variation was 5%. Vitamins A and E and the carotene fraction

ADDRESSES: Cardiovascular Research Unit, Department of Cardiology and Medicine (RIE), University of Edinburgh (R. A. Riemersma, PhD, Prof D. A. Wood, MRCP,* Prof M. F. Oliver, FRCP); Medical Statistics Unit, Medical School, Edinburgh, UK (R. A. Elton, PhD, C. C. A. Macintyre, MSc); and Vitamin Unit, Institute of Biochemistry and Molecular Biology, University of Berne, Switzerland (Prof K. F. Gey, MD). Present addresses: *Preventive Cardiology, Medicine I, University of Southampton; †Wynn Institute for Metabolic Research, London. Correspondence to Dr R. A. Riemersma, Cardiovascular Research Unit, University of Edinburgh, George Square, Edinburgh EH8 9XF, UK.

TABLE I—RISK FACTORS FOR CHD IN CONTROLS AND CASES

	Mean (SEM)	
	Controls (n = 430)	Cases (n = 125)
Age (yr)	47.8 (0.3)	46.8 (0.6)
% current cigarette smokers	29%	46%*
Cholesterol (mmol/l)	6.27 (0.06)	6.19 (0.11)
HDL cholesterol (mmol/l)	1.18 (0.02)	1.13 (0.03)
Weight/height ² (kg/m ²)	25.2 (0.2)	25.9 (0.5)
Blood pressure (mm Hg)	137 (1)/84 (1)	140 (2)/86 (1)

Data reproduced from ref 2. * $p < 0.01$.

(predominantly beta-carotene) were extracted into *n*-hexane and analysed by automated high performance liquid chromatography with a 'Lichrosorb Si 60-5 μ m' column.⁶ Vitamin A and carotene peaks were detected spectrophotometrically at 313 nm and 436 nm, respectively. A fluorometric detector (excitation 290 nm, emission 330 nm) was used for the detection of vitamin E. The peaks were integrated by means of a Perkin-Elmer Sigma 10B system. The coefficients of variation for the estimations of vitamin A and E and carotene were 3.3%, 3.0%, and 1.8%, respectively. Plasma vitamin E concentration correlated strongly with circulating total cholesterol concentrations ($r = 0.61$, $p < 0.001$), so results for vitamin E are also expressed as vitamin E/cholesterol (μ mol/mmol).

All laboratory analyses were carried out on samples from cases and controls simultaneously by laboratory staff unaware of the status of individual samples.

Statistical comparisons between groups were done by means of *t* tests and analysis of variance for more than two groups. The analysis of variance for smoking categories was supplemented with pairwise *t* tests with a Bonferroni correction to allow for the examination of six sets of comparisons. For vitamin E and carotene a square-root transformation was used to compare mean values, since the distribution of the data was positively skewed (log transformation of these variables resulted in a negatively skewed distribution). Logistic regression was used to investigate the relations among angina pectoris, vitamins, fatty acids, and risk factors for CHD. The triglyceride measurements were log transformed before analysis. Each vitamin was included separately in a multiple logistic regression with all the risk factors (whether or not they were

significant) and the statistical significance of the overall trend in odds ratios is presented.

The adjusted odds ratios for angina were calculated in relation to the distribution of the vitamin concentrations in the healthy control population. The vitamin concentrations of cases, expressed as a categorical variable (1-5: quintile of the control data whose limits included the result) were fitted in a model with all the risk factors. The odds ratios were calculated as the exponential of the four coefficients that resulted, and the exponential of the confidence intervals of these coefficients were the confidence intervals of the odds ratios (95% CI). The possibility of an interaction between vitamin E and adipose linoleic acid content was examined. The statistical analyses were made by means of the BMDP package (BMDP Statistical Software 1983, University of California Press).

Results

Risk factors for CHD in angina cases and controls are shown in table I. The only significant difference between the groups was in the proportion of cigarette smokers ($p < 0.01$). The cases were significantly shorter ($p < 0.05$) but there was no difference in weight or weight/height index.

Mean plasma concentrations of vitamin C, carotene (predominantly beta-carotene), and vitamin E adjusted for plasma cholesterol (in view of the relation between the two) were lower in angina cases than in controls (table II). There was no difference in plasma vitamin A concentrations.

We examined the relations among plasma vitamin concentrations and CHD risk factors in the healthy controls. Cigarette smokers had significantly lower levels of carotene and vitamin C than subjects who had never smoked (table III). There was no significant difference in any vitamin concentration between ex-smokers (cigarettes, pipe, and cigars) and never smokers, but ex-smokers had significantly higher vitamin C and vitamin E/cholesterol concentrations than current cigarette smokers. Pipe and cigar smokers also had significantly higher vitamin C levels than cigarette smokers.

Vitamin A and E concentrations were positively related to total cholesterol (Pearson correlation coefficients [*r*] 0.28 and 0.61, respectively; $p < 0.001$) and triglycerides ($r = 0.32$ and 0.41; $p < 0.001$) but not to HDL cholesterol. Plasma carotene was inversely related to non-fasting triglyceride concentration ($r = -0.25$; $p < 0.001$). The plasma concentrations of vitamin E and vitamin C were positively related to adipose linoleate content ($r = 0.31$ and 0.34; $p < 0.001$), as was vitamin E/cholesterol ($r = 0.48$; $p < 0.001$). Vitamin A was positively related to diastolic (and systolic) blood pressure ($r = 0.24$; $p < 0.001$). There were no significant correlations with age or weight/height index. The concentrations of all the vitamins showed significant seasonal trends (table IV).

The odds ratios for angina, relative to the highest quintile of the distribution of plasma vitamin concentrations in the control population are shown in table V. The odds ratio for angina in the lowest quintile of vitamin E distribution rose from 2.51 to 2.68 after adjustment for cholesterol and other CHD risk factors and the overall trend was significant ($p = 0.02$). The results were similar when vitamin E/

TABLE II—PLASMA VITAMIN CONCENTRATIONS

	Mean (SEM)		p
	Controls (n = 394)	Cases (n = 110)	
Vitamin A (μ mol/l)	2.32 (0.03)	2.29 (0.05)	NS
Carotene (μ mol/l)	0.49 (0.02)	0.30 (0.03)	<0.001
Vitamin C (μ mol/l)	35.3 (1.1)	28.1 (2.1)	<0.01
Vitamin E (μ mol/l)	24.0 (0.3)	22.7 (0.6)	NS
Vitamin E/cholesterol (μ mol/mmol)	3.86 (0.04)	3.66 (0.08)	<0.01

NS = not significant.

TABLE III—PLASMA VITAMIN CONCENTRATIONS IN RELATION TO REPORTED SMOKING HABIT IN CONTROLS

	Mean (SEM) in μ mol/l*				
	Vitamin A	Carotene	Vitamin C	Vitamin E	Vitamin E/ cholesterol
Never smoked (n = 132)	2.27 (0.04)	0.53 (0.03)*	40.9 (1.8)†	23.5 (0.5)	3.88 (0.06)
Ex-smokers (n = 87)	2.35 (0.05)	0.50 (0.03)	42.6 (2.4)†	25.5 (0.7)	4.12 (0.08)†
Pipe/cigar smokers (n = 44)	2.35 (0.06)	0.53 (0.05)	38.4 (3.4)†	24.3 (1.2)	3.93 (0.13)
Cigarette smokers (n = 127)	2.33 (0.05)	0.42 (0.02)	24.1 (1.9)	23.3 (0.6)	3.63 (0.07)

*Except vitamin E/cholesterol which is in μ mol/mmol.
†For significance of differences (pairwise *t* test with Bonferroni correction) from cigarette smokers: * $p < 0.01$; † $p < 0.001$ after normalisation. No data on 6 subjects.

TABLE IV—SEASONAL TRENDS IN PLASMA VITAMIN CONCENTRATIONS IN CONTROLS

	Highest	Lowest	Difference
Vitamin A	November	May	12% ($p < 0.001$)
Carotene	November	May	37% ($p < 0.01$)
Vitamin C	August	February	48% ($p < 0.001$)
Vitamin E	December	June	15% ($p < 0.001$)

TABLE V—ODDS RATIOS FOR ANGINA PECTORIS BY QUINTILES OF PLASMA VITAMIN CONCENTRATIONS IN CONTROLS, WITH AND WITHOUT ADJUSTMENT* FOR CHD RISK FACTORS

—	Vitamin A		Carotene		Vitamin C		Vitamin E	
	μmol/l	Odds ratio (95% CI)	μmol/l	Odds ratio (95% CI)	μmol/l	Odds ratio (95% CI)	μmol/l	Odds ratio (95% CI)
<i>Quintile 1</i>	<1.93		<0.26		<13.1		<18.9	
Unadjusted	..	1.67 (0.86–3.26)	..	2.64 (1.32–5.29)	..	2.35 (1.16–4.78)	..	2.51 (1.24–5.10)
Adjusted	..	2.73 (1.24–6.02)	..	1.41 (0.63–3.13)	..	1.63 (0.76–3.49)	..	2.68 (1.07–6.70)
<i>Quintile 2</i>	1.93–2.16		0.26–0.37		13.1–23.8		19.0–21.8	
Unadjusted	..	1.11 (0.53–2.33)	..	1.42 (0.68–2.95)	..	1.66 (0.80–3.42)	..	1.04 (0.44–2.44)
Adjusted	..	1.34 (0.60–2.98)	..	1.00 (0.44–2.23)	..	1.32 (0.60–2.38)	..	1.69 (0.72–4.00)
<i>Quintile 3</i>	2.17–2.37		0.38–0.49		23.9–41.4		21.9–24.2	
Unadjusted	..	1.11 (0.54–2.27)	..	1.30 (0.70–2.17)	..	1.75 (0.79–3.92)	..	1.00 (0.43–2.35)
Adjusted	..	1.58 (0.72–3.45)	..	0.98 (0.43–2.22)	..	1.56 (0.72–3.36)	..	1.18 (0.49–2.81)
<i>Quintile 4</i>	2.38–2.68		0.50–0.67		41.5–57.3		24.3–28.1	
Unadjusted	..	1.39 (0.70–2.75)	..	1.16 (0.53–2.53)	..	0.81 (0.36–1.81)	..	1.63 (0.77–3.43)
Adjusted	..	1.84 (0.88–3.88)	..	0.95 (0.43–2.12)	..	0.87 (0.70–2.04)	..	1.64 (0.76–3.51)
<i>Quintile 5</i>	≥2.69		≥0.68		≥57.4		≥28.2	
Unadjusted	..	1.00	..	1.00	..	1.00	..	1.00
Adjusted	..	1.00	..	1.00	..	1.00	..	1.00

*By logistic regression for age, systolic and diastolic blood pressure, cholesterol, HDL cholesterol, non-fasting triglycerides, relative weight, smoking habit, and season for 105 cases and 382 controls with complete data. Linear trend after adjustment in logistic regression not statistically significant, except for vitamin E ($p=0.02$).

cholesterol ratios were used (adjusted odds ratio 2.21 [1.05–4.67]; overall trend $p<0.01$). The unadjusted odds ratios for angina subjects with the lowest concentrations of vitamin C and of carotene were 2.35 (1.16–4.78) and 2.64 (1.32–5.29), respectively, but the strength of these inverse relations was reduced and they were no longer significant ($p=0.09$ and 0.40, respectively) after adjustment for smoking and other risk factors. The odds ratios for angina by vitamin A and vitamin A/cholesterol (not shown) concentrations were not significant.

We have previously reported an inverse relation between adipose linoleic acid and platelet eicosapentaenoic acid content and the risk of angina for this population.² The inverse relation between plasma vitamin E concentration and the likelihood of angina was therefore examined in relation to these fatty acids. When they were included in the logistic analysis for vitamin E, adipose tissue linoleate content ($p<0.001$) and platelet eicosapentaenoate content ($p<0.01$) each made an independent contribution to the explanation of angina, but plasma vitamin E concentration did not ($p=0.09$). There was no significant interaction between adipose linoleic acid and vitamin E ($p=0.52$).

Discussion

In this population case-control study low plasma concentrations of vitamins E and C and carotene were related to an increased risk of angina pectoris in men. For plasma vitamin E concentration the relation remained significant after adjustment for age, blood pressure, total and HDL cholesterol, non-fasting triglycerides, relative weight, and smoking status. The association between low plasma vitamin C levels and angina was confounded by cigarette smoking. Vitamin C levels are, as we confirmed, lower in cigarette smokers than in non-smokers. In the National Health and Nutritional Examination Survey⁷ vitamin C intake and plasma concentrations were lowest in those who smoked most cigarettes. Furthermore, smoking may interfere with vitamin C absorption and increase vitamin C requirements.⁸

We found no significant difference in vitamin E/cholesterol between cigarette smokers and non-smokers,⁹ though ex-smokers had significantly higher vitamin E/cholesterol ratios than current cigarette smokers. One explanation for this finding could be a change in dietary

habit after stopping smoking; a dietary survey in this population showed that ex-smokers ate more polyunsaturated fat (vitamin E rich) than those who were still smoking cigarettes.¹⁰ Our cigarette smokers also had significantly lower concentrations of carotene than non-smokers, which confirms the findings of Stryker and colleagues.¹¹ The concentration of vitamin E, which is transported in the bloodstream by lipoprotein particles, was closely correlated with that of total cholesterol and derived LDL cholesterol.¹² There were no strong correlations between plasma concentrations of antioxidant vitamins and other classic risk factors.

Adipose tissue linoleic acid and platelet eicosapentaenoic acid content are inversely related to the risk of angina pectoris in this population.² Plasma vitamin E was positively correlated with adipose tissue linoleate,¹³ but not with platelet eicosapentaenoic acid. So subjects with low plasma vitamin E concentrations also tend to have low adipose tissue linoleate, reflecting long-term low dietary intake of this polyunsaturated essential fatty acid. A dietary survey in Scotland showed that middle-aged men have low consumption of polyunsaturated oils and cereal fibre,^{10,14} but vitamin intake was not measured. Although adipose linoleate and plasma vitamin E were both inversely related to likelihood of angina in our study, the relation between low vitamin E and angina is important since it is independent of the generally accepted CHD risk factors.

Our angina cases were defined by a self-administered WHO chest pain questionnaire and were unaware of the nature of their chest pain. They were therefore unlikely to have changed their dietary habits. Of course, a positive response to the WHO questionnaire is not the same as a doctor's diagnosis of angina, but nor are patients diagnosed by their general practitioners necessarily representative of all patients with angina. We used the WHO questionnaire as a valid and reproducible measure of angina in the population which is not subject to the bias of self-referral or the large variation between and within observers associated with doctors' diagnoses. Some of the subjects positive on this questionnaire will not have CHD, but this is a conservative bias in the study. If there is a true inverse relation between plasma vitamin concentration and risk of angina, the inclusion of subjects without angina will dilute this estimate.

The evidence from cross-cultural studies linking low plasma antioxidants with CHD has been equivocal. Our study¹³ of healthy middle-aged men in Scotland, Finland, and Italy showed no consistent relation between plasma concentrations of carotene or vitamins A, C, and E and CHD mortality statistics for these populations, though the vitamin E/cholesterol ratio was generally lower in northern Europe, where CHD mortality is higher. These studies are being extended within the MONICA framework. This study was carried out over several years and repeat analyses of men in Finland have shown pronounced rises in plasma vitamin E and C concentrations between spring 1983 and spring 1987.

Within-population studies have shown an inverse relation between vitamin consumption and cardiovascular mortality. In the USA, industrial vitamin C production is inversely related to CHD mortality over the past 20 years.¹⁵ Regional standardised mortality ratios for CHD in the UK relate inversely to calculated vitamin C intake (National Food Survey), reflecting a long-established regional gradient in lifestyle and social circumstance.¹⁶ There is a similar inverse and powerful relation between the consumption of fresh fruit and green vegetables and mortality from all cerebrovascular disease, independent of social class.¹⁷ Middle-aged Scottish men eat very little fruit and green vegetables.¹⁸ However, material deprivation predicts CHD mortality better than social class^{19,20} and preliminary data have shown that the relations between dietary factors and material deprivation are not identical to those that correlate with social class.

There have been only a few other studies of vitamins and their relation to CHD in individuals. Ramirez and Flowers²¹ found that men with significant coronary artery obstructions and regional wall kinetic abnormalities had lower leucocyte ascorbic acid levels than those with normal arteriograms, irrespective of smoking status. On the other hand, Salonen and colleagues²² found that neither plasma vitamin C nor cholesterol-adjusted vitamin E differed between those with and without CHD defined on the basis of symptoms, a history of CHD, or objective evidence of ischaemia on a bicycle ergometer exercise test. The fact that liver vitamin A content does not differ significantly between subjects dying from CHD and from accidents²³ and the possibility that patients with established CHD may change their diet, makes the interpretation of necropsy and chronic CHD studies difficult, if not impossible. Prospective studies of the relation between vitamin levels and CHD mortality in individuals, both men and women, have found no significant relations.^{24,25}

We should emphasise that the inverse relation we found may not apply to other communities with a high incidence of CHD.¹³

How could low plasma and (presumably) low tissue levels of naturally occurring antioxidants relate to CHD? Formation of foam cells from monocytes/macrophages is favoured when LDL is in the oxidised or modified form.¹ Probucol, a lipid-lowering drug with antioxidant properties, protects LDL against oxidative modification by endothelial cells in culture²⁷ and reduces aortic atheromatous lesions in a rabbit model of hyperlipidaemia, an effect not explained by changes in lipoprotein concentrations.²⁸ Whether a low concentration of naturally occurring antioxidants favours the formation of oxidised LDL has yet to be shown, but the addition of vitamin E to cell cultures blocks the oxidative modification of LDL.²⁹

An increased tendency to peroxidation of polyunsaturated fatty acids resulting from a reduction in antioxidant availability might favour thrombosis by allowing saturated fatty acids, which are more thrombotic,³⁰ to have an unbalanced effect. The myocardium may also be adversely affected after periods of ischaemia if tissue concentrations of free radical scavengers, such as vitamins E and C, are low. During ischaemic reperfusion, oxygen free radicals are produced and these may lead to further tissue damage and reperfusion injury,³¹ the development of arrhythmias,³² and depression of myocardial contractility.³³

The importance of oxidative modification of LDL and increased atherosclerosis, thrombosis, and myocardial ischaemic damage in leading to CHD may depend on the fatty acid composition of the diet. Polyunsaturated fatty acids are very vulnerable to free radical attack. Lipid peroxidation can become autocatalytic, but the chain-reaction can be prevented by the action of vitamin E. Vitamin C has a sparing activity on vitamin E. Diets low in linoleic acid tend to be low in vitamin E (and also C).

Our study cannot of course elucidate the mechanisms whereby low plasma vitamin E and C may predispose to CHD. The evidence from our retrospective study is sufficiently strong to justify further studies of essential antioxidants. An intervention trial with vitamin supplements is the most conclusive way to test the nature of the association between low plasma antioxidants and CHD.

Antioxidants are more easily destroyed by food processing than polyunsaturated fatty acids.³⁴ This fact, combined with a habitual low intake of vitamins E and C, suggests that some populations with a high incidence of CHD should supplement their eating habits with more cereals, vitamin-E-rich oils, vegetables, and fruit.

This study was supported by the British Heart Foundation, the Wellcome Trust, Scottish Home and Health Department, and the Scottish Chest Heart and Stroke Association. A preliminary report of the vitamin E findings was presented to the New York Academy of Sciences (*Ann NY Acad Sci* 1989; 570: 291-95).

REFERENCES

- Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989; 320: 915-24.
- Wood DA, Riemersma RA, Butler S, et al. Linoleic and eicosapentaenoic acids in adipose tissue and platelets and risk of coronary heart disease. *Lancet* 1987; i: 177-80.
- Rose G, McCartney P, Reid DD. Self administration of questionnaire on chest pain and intermittent claudication. *Br J Prevent Soc Med* 1977; 31: 42-48.
- Wood DA, Butler S, Riemersma RA, et al. Adipose tissue and platelet fatty acids and coronary heart disease in Scottish men. *Lancet* 1984; ii: 117-21.
- Brubacher G, Vuilleumier JP. Vitamin C. In: Curtius HC, Roth M, eds. *Clinical biochemistry. Principles and methods*, vol 2. Berlin: de Gruyter, 1974: 989-97.
- Vuilleumier JP, Keller HE, Gysel D, Hunziker F. Clinical chemical methods for the routine assessment of the vitamin status in human population. Part 1: The fat soluble vitamins A and E, and beta-carotene. *Int J Vit Nutr Res* 1983; 53: 265-72.
- Schectman G, Byrd JC, Gruchow HW. The influence of smoking on vitamin C status in adults. *Am J Publ Health* 1989; 79: 158-62.
- Kallner AB, Hartman D, Hornig DH. On the requirements of ascorbic acid in man: steady state turnover and body pool in smokers. *Am J Clin Nutr* 1981; 34: 1347-55.
- Ellis N, Lloyd B, Lloyd RS, Clayton BE. Selenium and vitamin E in relation to risk factors for coronary heart disease. *J Clin Pathol* 1984; 37: 200-26.
- Fulton M, Thomson M, Elton RA, Brown S, Wood DA, Oliver MF. Cigarette smoking, social class and nutrient intake: relevance to coronary heart disease. *Eur J Clin Nutr* 1988; 42: 797-803.