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ORIGINAL COMMUNICATION

The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART)

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Objective: To assess the long-term effect of dietary advice on diet and mortality after a randomised trial of men with a recent history of myocardial infarction.
Design: Questionnaire survey and mortality follow-up after a trial of dietary advice.
Setting: Twenty-one hospitals in south Wales and south-west England.
Subjects: Former participants in the Diet and Reinfarction Trial.
Main outcome measures: Current fish intake and cereal fibre intake. All-cause mortality, stroke mortality and coronary mortality.
Results: By February 2000, after 21 147 person years of follow-up, 1083 (53%) of the men had died. Completed questionnaires were obtained from 879 (85%) of the 1030 men alive at the beginning of 1999. Relative increases in fish and fibre intake were still present at 10 y but were much smaller. The early reduction in all-cause mortality observed in those given fish advice (unadjusted hazard 0.70 (95% CI 0.54, 0.92)) was followed by an increased risk over the next 3 y (unadjusted hazard 1.31 (95% CI 1.01, 1.70). Fat and fibre advice had no clear effect on coronary or all-cause mortality. The risk of stroke death was increased in the fat advice group — the overall unadjusted hazard was 2.03 (95% CI 1.14, 3.63).
Conclusions: In this follow-up of a trial of intensive dietary advice following myocardial infarction we did not observe any substantial long-term survival benefit. Further trials of fish and fibre advice are feasible and necessary to clarify the role of these foods in coronary disease.
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Keywords: fish; fibre; fat; dietary advice; randomised controlled trial; all-cause mortality; coronary heart disease; stroke

Introduction

Studies suggest that diets low in saturated fat (Hooper *et al*, 2001) high in fibre (Anderson and Hanna, 1999) and high in fish (particularly fatty fish) (Marckmann & Gronbæk, 2000) are associated with reduced risk of coronary disease. Whether dietary advice to people with coronary disease alters diet and improves long-term survival is unclear.

We followed up former participants in the Diet and Reinfarction Trial (DART) (Burr *et al*, 1989a,b; Fehily *et al*, 1989) to determine their current diet and subsequent mortality.

Methods

The recruitment and methods of the Diet and Reinfarction Trial (DART) have been described in detail previously (Burr *et al*, 1989a,b; Fehily *et al*, 1989). Briefly, between 1983 and

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1987 2033 men aged under 70 who had survived a myocardial infarction were enrolled in the study. They were recruited from 21 hospitals in south Wales and the south-west of England (Burr *et al*, 1989b).

Subjects were seen in their homes, usually with their wives, by a nutritionist and randomly allocated to one of three study diets in a factorial design. Those allocated to receive no advice were given a sensible eating sheet, which did not include specific advice on any of the proposed interventions. Subjects were visited again after 1, 3 and 6 months. Thereafter they were contacted at 3 monthly intervals until 2 y after entry to the trial.

Those randomised to fish advice were encouraged to eat two portions of fatty fish a week and as much other fish as they could manage. Those unable to eat this amount of fish were offered fish oil capsules (MaxEPA). Those randomised to fibre advice were encouraged to eat at least six slices of wholemeal bread per day, or an equivalent amount of cereal fibre from a mixture of wholemeal bread, high-fibre breakfast cereals and wheat bran. The advice given to those in the fat advice group was complex. The advice aimed to achieve a reduction in total fat intake and increase in the (polyunsaturated fat/saturated fat) P/S ratio.

At 2 y the percentage of energy from fat was around 35% in those not given fat advice and just over 32% in those given fat advice. The P/S ratio was around 0.4 in those not given fat advice compared to just under 0.8 in the fat advice group. Cereal fibre intake in the fibre advice group was 17 g per day and 9 g per day in those not given fibre advice. Reported fatty fish intake was 35 g per day in the fish advice group and around 9 g per day in those not given fish advice. Percentages of linoleic acid and eicosapentaenoic acid in plasma total fatty acids were measured by gas chromotography in a subset of the men. The differences were consistent with the reported dietary changes (Burr *et al*, 1989a,b; Fehily *et al*, 1989). In June 1989 at the end of the study subjects were sent a letter outlining the results of the study, recommending that they continue with their allocated diet and advising all men to eat more fatty fish.

Between 1999 and 2000 a brief self-completion questionnaire, with pre-paid addressed envelope, was sent to all surviving participants. Where the man had moved the Health Authority was contacted and asked for the new GP's name and address and the GP was asked to forward the questionnaire. If the man did not return the questionnaire two further questionnaires were sent out. Men who still failed to respond were contacted by telephone and the questionnaire administered over the telephone. Non-responding men still resident in south-west England or south Wales, who could not be contacted by telephone, were visited at home and the questionnaire administered by the interviewer.

The questionnaire enquired about current health, disease experience, current and past smoking, current medication and current weight. The questionnaire included relevant sections from the food frequency questionnaire previously calibrated for use in this population. These sections enquired about the frequency of consumption of fish, bread and cereals in an 'average week' and what dietary supplements the man had taken regularly in the last year. Portion size estimates used during the trial were used to estimate fish intake and dietary fibre intake from cereals. The dietary data collected did not allow estimation of current intake of dietary fat or P/S ratio.

All men in the trial had been flagged with the NHS central register. Additional men who had died were identified during the course of the questionnaire follow-up. Confirmation of the date and cause of death was sought from the NHS central register. Death certificates were obtained for almost all men who died before the end of February 2000.

The data were analysed using STATA 5.0 (Stata Corporation, 1997). Analyses concentrated on comparisons between men given and not given fish, fat or fibre advice. Differences in current fish intake, fibre intake, weight, smoking, medication use and vitamin supplement use were assessed using chi-squared and unpaired *t*-tests. Cox's proportional hazards regression was used to compare survival between different dietary advice groups and to adjust for the effects of possible confounding factors.

Results

By the end of February 2000 1083 (53%) men enrolled in the study had died after a total of 21 147 person-years of observation. Of these deaths 738 (68%) were attributed to coronary heart disease and 52 (5%) were attributed to stroke.

Completed questionnaires were obtained from 879 of the surviving men. Before the questionnaire follow-up commenced (the beginning of January 1999) 1030 of the participants were still alive and by the end of the questionnaire follow-up (the end of December 2000) 972 of the participants were still alive. Some of the men died before they received the questionnaire or before they could be contacted by phone or visited. The response rate, thus, lies somewhere between 85% and 90%.

The characteristics of the 879 surviving men by the dietary advice group they were randomised to are shown in Table 1. Data were not available on diet in one man, vitamin use in three, smoking status in four men and self-reported weight in 15 men. There were no differences in self-reported weight, current smoking, medication use, aspirin use, or dietary supplement use. The distributions of intake of total fish, fatty fish and fibre were all skewed. We have presented the means and standard deviations to allow comparison with earlier reports from this study. However, the results were essentially unchanged when the analyses were repeated using non-parametric tests (data not shown). Those allocated to fish advice reported eating more fish and in particular more fatty fish — although the differences were substantially reduced compared to those reported at 2 y. In addition, they were more likely to take fish oil supplements and although only a few were taking Maxepa capsules, those allocated to

Table 1 Characteristics of surviving men enrolled in the Diet and Reinfarction Trial (DART) by dietary advice group 1999–2000

	Fish advice (n = 447)	*No fish advice (n = 432)*	P-value	*Fat advice (n = 440)*	*No fat advice (n = 439)*	P-value	*Fibre advice (n = 443)*	*No fibre advice (n = 436)*	P-value
				Mean (s.d.)					
Self-reported weight (kg)	77.8 (12.1)	78.7 (13.2)	0.33	78.3 (12.6)	78.2 (12.7)	0.84	78.5 (12.7)	78.0 (12.6)	0.63
Fish intake (g/day)	43.6 (37.8)	36.9 (33.7)	<0.01	41.3 (37.2)	39.3 (34.8)	0.42	39.7 (34.2)	40.9 (37.8)	0.63
Fatty fish intake (g/day)	20.7 (26.2)	13.2 (20.6)	<0.01	18.0 (26.0)	16.0 (21.6)	0.24	17.2 (23.9)	16.8 (24.0)	0.82
Cereal fibre intake (g/day)	5.6 (4.8)	5.6 (5.1)	0.94	5.6 (5.1)	5.6 (4.9)	0.91	6.2 (5.4)	5.0 (4.4)	<0.01
				Number (%)					
Current smokers	76 (17.0)	83 (19.3)	0.39	77 (17.5)	82 (18.8)	0.64	91 (20.6)	68 (15.6)	0.06
Dietary supplement takers	148 (33.2)	143 (33.2)	1.00	145 (33.0)	146 (33.3)	0.92	150 (33.9)	141 (32.5)	0.67
Fish oil supplement takers	120 (26.9)	83 (19.3)	<0.01	100 (22.8)	103 (23.5)	0.80	102 (23.0)	101 (23.3)	0.93
Maxepa takers	10 (2.3)	2 (0.5)	0.02	8 (1.8)	4 (0.9)	0.25	8 (1.8)	4 (0.9)	0.26
Taking regular medication	412 (92.2)	408 (94.2)	0.23	409 (93.0)	411 (93.4)	0.79	415 (93.5)	405 (92.9)	0.73
Taking aspirin	265 (59.3)	248 (57.3)	0.55	258 (58.6)	255 (58.0)	0.84	246 (55.4)	267 (61.2)	0.08

Table 2 Mortality from coronary disease, stroke and all causes in men who received advice to eat more fish compared with those who did not in the Diet and Reinfarction Trial (DART) 1983–2000

		Hazard (CI)	
Hazard by follow-up period in years	*Number of deaths advice/no advice*	*Crude hazard*	*Adjusted hazard*[a]
All-cause mortality			
0–2	94/131	0.70 (0.54, 0.92)	0.73 (0.56, 0.95)
2–5	130/97	1.31 (1.01, 1.70)	1.31 (1.01, 1.71)
5–10	163/159	1.02 (0.82, 1.27)	1.02 (0.82, 1.27)
10+	143/166	0.84 (0.68, 1.06)	0.85 (0.68, 1.07)
Overall	530/553	0.94 (0.84, 1.06)	0.95 (0.85, 1.07)
Coronary heart disease			
0–2	78/117	0.65 (0.49, 0.87)	0.68 (0.51, 0.91)
2–5	83/75	1.08 (0.79, 1.47)	1.08 (0.79, 1.48)
5–10	107/104	1.03 (0.78, 1.35)	1.04 (0.79, 1.36)
10+	86/88	0.96 (0.71, 1.29)	0.98 (0.72, 1.32)
Overall	354/384	0.91 (0.79, 1.05)	0.92 (0.80, 1.07)
Stroke			
0–2	5/2	—	—
2–5	2/0	—	—
5–10	12/7	1.71 (0.67, 4.34)	1.57 (0.61, 4.03)
10+	10/14	0.70 (0.31, 1.57)	0.71 (0.32, 1.61)
Overall	29/23	1.24 (0.72, 2.15)	1.23 (0.71, 2.14)

[a]Adjusted for history of myocardial infarction, angina, hypertension at baseline; X-ray evidence of cardiomegaly, pulmonary congestion or pulmonary oedema at baseline; and treatment (at entry) with β-blockers, other anti-hypertensives, digoxin/anti-arrhythmics, or anticoagulants.

receive fish advice were more likely to be taking Maxepa. Those allocated to receive fibre advice had a significantly higher fibre intake although the absolute difference was small.

The effects of dietary advice on mortality attributed to coronary heart disease, stroke and all causes are shown in Tables 2–4. The hazard is calculated for the whole of the follow-up period and four time periods that contained approximately equal numbers of deaths: the first 2 y, the next 3 y, the next 5 y and follow-up beyond 10 y. We have not included the hazard for stroke for the first two time periods as these estimates were based on seven and two events respectively. The crude hazards are essentially unaltered after adjustment for the baseline variables used in the original report (Burr *et al*, 1989a).

Those given fish advice had reduced all cause mortality at 2 y (as reported previously) but increased all-cause mortality in the following time periods such that by the end of the follow-up there was little difference in overall mortality between the two groups. Unlike the observed reduction in all-cause mortality in the first 2 y, which was largely explicable by a reduction in coronary death, the observed excess in all-cause mortality in the period from 2 to 5 y was largely due to an excess in deaths not attributed to coronary disease. For coronary death there was a reduced hazard in the first 2 y and thereafter a fairly constant hazard such that there was still

Table 3 Mortality from coronary disease, stroke and all causes in men who received advice to eat less fat (and to increase intake of polyunsaturates relative to saturates) compared with those who did not in the Diet and Reinfarction Trial (DART) 1983–2000

		Hazard (CI)	
Hazard by follow-up period in years	*Number of deaths advice/no advice*	*Crude hazard*	*Adjusted hazard*[a]
All cause mortality			
0–2	111/114	0.97 (0.74, 1.25)	0.98 (0.76, 1.28)
2–5	110/117	0.94 (0.72, 1.21)	0.92 (0.71, 1.19)
5–10	161/161	0.98 (0.79, 1.22)	0.97 (0.78, 1.21)
10+	157/152	1.02 (0.81, 1.27)	1.00 (0.80, 1.26)
Overall	539/544	0.98 (0.87, 1.10)	0.96 (0.86, 1.09)
Coronary heart disease			
0–2	97/98	0.98 (0.74, 1.30)	1.00 (0.75, 1.32)
2–5	80/78	1.02 (0.75, 1.40)	1.00 (0.73, 1.37)
5–10	100/111	0.89 (0.68, 1.16)	0.87 (0.66, 1.14)
10+	76/98	0.76 (0.57, 1.03)	0.74 (0.55, 1.00)
Overall	353/385	0.91 (0.79, 1.05)	0.89 (0.77, 1.02)
Stroke			
0–2	7	—	—
2–5	2	—	—
5–10	12/7	1.69 (0.67, 4.29)	1.68 (0.66, 4.28)
10+	18/6	2.97 (1.18, 7.48)	3.13 (1.24, 7.90)
overall	35/17	2.03 (1.14, 3.63)	2.01 (1.12, 3.59)

[a]Adjusted for history of myocardial infarction, angina, hypertension at baseline; X-ray evidence of cardiomegaly, pulmonary congestion or pulmonary oedema at baseline; and treatment (at entry) with β-blockers, other anti-hypertensives, digoxin/anti-arrhythmics, or anticoagulants.

Table 4 Mortality from coronary disease, stroke and all causes in men who received advice to eat more cereal fibre compared with those who did not in the Diet and Reinfarction Trial (DART) 1983–2000

		Hazard (CI)	
Hazard by follow-up period in years	*Number of deaths advice/no advice*	*Crude hazard*	*Adjusted hazard*[a]
All-cause mortality			
0–2	123/102	1.22 (0.94, 1.59)	1.29 (0.99, 1.67)
2–5	120/107	1.17 (0.90, 1.52)	1.22 (0.94, 1.59)
5–10	150/172	0.90 (0.72, 1.12)	0.92 (0.74, 1.15)
10+	150/159	0.96 (0.77, 1.20)	0.97 (0.78, 1.22)
Overall	543/540	1.03 (0.91, 1.16)	1.07 (0.95, 1.20)
Coronary Heart Disease			
0–2	109/86	1.28 (0.97, 1.70)	1.35 (1.02, 1.80)
2–5	85/73	1.21 (0.89, 1.66)	1.27 (0.93, 1.75)
5–10	100/111	0.92 (0.71, 1.21)	0.96 (0.73, 1.26)
10+	83/91	0.93 (0.69, 1.25)	0.94 (0.70, 1.27)
Overall	377/361	1.07 (0.92, 1.23)	1.11 (0.96, 1.29)
Stroke			
0–2	7	—	—
2–5	2	—	—
5–10	10/9	1.14 (0.47, 2.82)	1.31 (0.53, 3.26)
10+	13/11	1.20 (0.54, 2.67)	1.13 (0.50, 2.56)
Overall	29/23	1.29 (0.74, 2.23)	1.34 (0.77, 2.32)

[a]Adjusted for history of myocardial infarction, angina, hypertension at baseline; X-ray evidence of cardiomegaly, pulmonary congestion or pulmonary oedema at baseline; and treatment (at entry) with β-blockers, other anti-hypertensives, digoxin/anti-arrhythmics, or anticoagulants.

some reduction in risk of coronary death at the end of the follow-up period. There was no clear effect on stroke, although the numbers were small.

There was no difference in overall survival in those who received fat advice. For coronary death there was no difference between the two groups in the first three time periods

but a suggestion that risk was reduced in the final follow-up period in those who received fat advice. For stroke, however, there was an increased risk in those who received fat advice, although the small numbers mean that the confidence intervals are wide.

All-cause mortality was increased in those given fibre advice in the first two time periods but reduced in the later time periods such that there was no long-term effect on survival. A similar pattern was present for coronary death. The risk of stroke death was slightly increased.

Discussion

Self-reported fatty fish intake and use of fish oil supplements were still higher (but much less than reported at 2 y) in former trial participants who had been given fish advice. Similarly self-reported cereal fibre intake was still slightly higher in those former participants who had received fibre advice. Unfortunately as no dietary data were collected between the end of the trial (1987–1989) and the present follow-up (1999–2000), we are unable to say how and when diet changed between then and now. It is also possible that the diets of those who survived are different from those who did not. The fact that overall mortality was largely unaffected by the dietary advice makes it less likely that the diets of survivors will be different from the diets of those that died, but we cannot discount this possibility.

We found no evidence that intensive and repeated advice to eat more fatty fish, less fat or more cereal fibre over a 2 y period had any sustained effect on all cause mortality. Men in the fat advice group were, however, at increased risk of stroke death. The large number of deaths from coronary heart disease and all causes means that we would have been able to detect modest differences in survival between dietary advice groups. Also nearly 70% of all deaths were attributed to coronary heart disease, which should be amenable to prevention.

The failure to observe a marked sustained reduction in mortality in men who received fish advice could be because fish does not reduce coronary or all-cause mortality with the original survival benefit at 2 y being merely a chance finding. This seems unlikely, particularly as another large trial of fish oil in people post myocardial infarction has reported a 14% reduction in all-cause mortality in those given fish oil capsules in a larger does than in DART (GISSI-Prevenzione Investigators, 1999). A more likely explanation is that

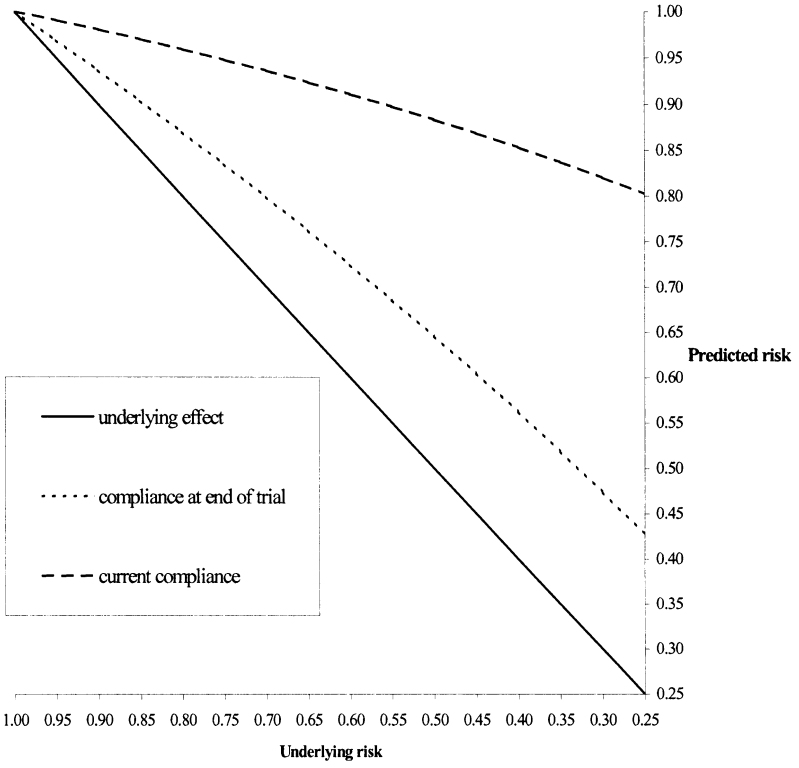

Figure 1 Predicted reduction in risk at various levels of compliance with fish advice. This figure compares the true effect of taking regular maxepa capsules or fatty fish at least once a week with that predicted at different levels of compliance. The underlying effect would be predicted if the compliance was 100% in the treatment group and 0% in the control group. At the end of the trial (1987–1989) compliance was 87% in the treatment group and 25% in the control group and current compliance (1999–2000) was 56 *vs* 37%. The predicted risk was calculated by multiplying the compliance by risk. For example the predicted risk for a compliance of 56 *vs* 37% and underlying effect size of 0.50 is $(0.56\times0.5)+(0.44\times1.0)/(0.37\times0.50)+(0.63\times1.0)=0.88$.

changes in compliance led to modest differences in fish intake between the two groups over most of the follow-up period. We have explored the likely effect of compliance further in Figure 1 by calculating the observed effect that we would have predicted for a given underlying effect and the compliance we observed. This shows that the modest long-term reductions in coronary and all-cause mortality are compatible with the mortality reductions observed at 2 y and with underlying reductions of 25% for all cause mortality and 35% for coronary mortality in those who continued to take the fish. Nevertheless it is interesting to speculate on why the marked benefits afforded by increased fish consumption in the first 2 y did not translate into a long-term survival benefit. It may be that fish consumption affords only acute protection through either a reduction in thrombotic tendency of platelets (by a reduction of ecosanoid synthesis), a reduction in platelet aggregation (through effects on prostaglandin metabolism) or a reduction in ischaemia-induced ventricular fibrillation (Kinsella *et al*, 1990; Billman *et al*, 1997). If this were the case the protection afforded by fish might well disappear or diminish when people stopped eating the fish. If fish intake reduced quickly at the end of the 2 y intervention period to current levels this might explain why the mortality benefit was not maintained. Alternatively, if fish consumption did not reduce abruptly, the protective effect of fish may be real but wane even if intake is sustained.

The increased risk of stroke in the fat advice group may well be a chance finding as the number of strokes was small and a number of statistical comparisons have been carried out. We did not attempt to estimate current fat intake but it seems unlikely that large differences in total fat intake emerged over time. The fat advice arm was complex and it may be that other dietary differences such as the reduction in the P/S ratio were maintained. Although these findings were unexpected, there is other epidemiological evidence that increased fat intake may be associated with reduced stroke risk from temporal analyses of Japanese stroke mortality (Kimura, 1983) and cohort studies in Japanese (McGee *et al*, 1985) and US populations (Gillman *et al*, 1997).

The fact that the initial increased risk of coronary death and deaths from all causes in men who were given advice to eat more cereal fibre was not maintained suggests that increased fibre intake is not harmful. The results of this study and two recently published trials of increased fibre intake in people with colorectal adenomas (Alberts *et al*, 2000; Bonithon-Kopp *et al*, 2000), however, suggest that increasing cereal fibre intake does not confer any immediate survival advantage.

There are a number of limitations to the dietary data collected in this survey. The dietary advice stopped after 2 y and all the surviving men received a letter encouraging them to eat more fatty fish and it is possible that this resulted in immediate dietary changes. The dietary data presented here were collected from at least 85% of survivors some years after the end of the 2 y of dietary advice when around half of the original participants had died. Diet was assessed with a limited number of questions that focused on fish and fibre intake. Questionnaire data were not collected on other aspects of current diet and objective biological measures of fish intake were not obtained. It is thus possible that we were unable to detect important differences in diet.

In conclusion, we found no evidence in this study that the intensive dietary advice given following a myocardial infarction conferred any substantial long-term survival benefit. It is not possible from these data to say whether continued fish intake confers a sustained survival benefit. There is a paucity of trial evidence to guide decisions about the value of dietary advice (and subsequent long-term dietary change) in people with coronary disease. As large long-term trials of advice to increase fish intake and cereal fibre intake are feasible further trials should be undertaken to clarify the role of these foods in people with coronary disease.

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