PAPERS AND ORIGINALS

Heart disease prevention project: a randomised controlled trial in industry

GEOFFREY ROSE, R F HELLER, HUGH TUNSTALL PEDOE, D G S CHRISTIE

Summary and conclusions

Twenty-four factories or other occupational groups, employing 18 210 men aged 40 to 59, were formed into matched pairs. One of each pair was allocated randomly to receive a five to six year programme of medical examinations and intervention to reduce the levels of the main coronary risk factors. Men at factories in the intervention group were given advice on dietary reduction of plasma cholesterol concentrations, stopping or reducing cigarette smoking, regular exercise for the sedentary and reduced energy intake for the overweight, and hypertension was treated. The programme was delivered mainly through existing occupational medical services, helped by a small central staff. Personal consultations were largely confined to men with a high risk of developing coronary heart disease. Changes in risk factors were assessed by regular standardised examinations of random samples of men. The spread of information by general propaganda proved easy, but a change in habits seemed to require personal contact. Small but significant reductions occurred, mainly in the high-risk group, but these were not sustained when pressure was relaxed.

Introduction

Epidemiological research has established that several easily measured personal characteristics can identify individuals with a heightened risk of developing coronary heart disease. Evidence that some of these factors are actual causes of disease has led expert committees in many countries to recommend measures for their control.[1] Such recommendations rest on assumptions that the risk factors are indeed causes, that the risk is reversible, and that advice on behavioural change will be accepted.

The Heart Disease Prevention Project was set up in 1971 to test these assumptions by discovering to what extent the major coronary risk factors can be changed in ordinary middle-aged men and what effect such changes have on incidence and mortality. The trial was set up in industry, where the growing pressures towards routine heart checks and preventive advice left many occupational physicians uncertain about the right policy to adopt.

Methods

The plan has been described already.[2] Twenty-four large industrial groups (mainly factories) were recruited and then paired according to type of industry and area. One of each pair was allocated at random to receive the intervention programme while the other served as a control. The original plan was for a United Kingdom trial comprising about 20 000 subjects from about 20 sites. Recruitment started in 1971 and was completed in 1973. The study was later extended, under the auspices of the World Health Organisation, to centres in Belgium, Italy, Poland, and Spain,[3] where recruitment continued until 1977. This report deals only with the United Kingdom trial.

The 24 factories or occupational groups represented a cross-section of light, medium, and heavy industry. Within each group the study included all men aged 40 to 59 regardless of their actual jobs, except in the two steel works in South Wales, where only office staff were included. The total number of subjects was 18 210 (9734 intervention, 8476 control). The mean age of the intervention group was 50·3 (±5·4) years and the control group 50·1 (±5·4) years.

INTERVENTION PROGRAMME

The programme comprised advice on dietary reduction of plasma cholesterol concentrations, stopping or reducing smoking, weight reduction, and daily exercise and treatment of hypertension.

All men, but particularly those with high cholesterol concentrations, were advised to lower their intake of saturated fat and cholesterol and to substitute soft (polyunsaturated) margarine and vegetable oil for hard fats. Men whose weight for height was 15% or more over the average for their age were also advised how to restrict their

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energy intake, particularly fat and sugar. Those whose work was sedentary and who were not taking regular exercise were recommended to walk briskly for 20 minutes daily or follow a system of graded calisthenics which we developed from the Canadian Air Force 5BX plan.

Men whose systolic blood pressures were 200 mm Hg or more (mean of four readings on two occasions) were referred to their general practitioners with a recommendation to treat. Those whose mean values were 160-199 mm Hg were treated by the occupational physician (with the general practitioner's agreement) with bendrofluazide 10 mg/day supplemented where necessary by reserpine 0·25 mg/day.

Intervention began with the offer of a screening examination, which was accepted by 86% of men. A team of nurses visited each factory in turn, using a standardised questionnaire and examination to assess major risk factors and detect symptoms or electrocardiographic signs of pre-existing heart disease.

HIGH-RISK GROUP

The risk factor results were used to calculate a simple coronary risk score.[3] Within each factory a cut-off score was determined such that it was exceeded by 12-15% of the examined men; these individuals, designated "high-risk," were recalled for consultations with the occupational physician, who advised or treated them individually. Each consultation lasted about 15 minutes, and in the first year there were on average four consultations per man.

Advice was reinforced with specially prepared booklets providing general information on heart disease and its prevention, diets for cholesterol and weight reduction, stopping smoking, and exercise. Each high-risk man was also asked to complete a diary record of his current eating and return it to the nurse. She then wrote him a letter of appropriate personalised advice; six weeks later she asked him to complete another diet record, to which she again sent a personal reply.

MASS ADVICE

The project's first aim was to evaluate a preventive programme capable of implementation by existing medical staff. This determined the maximum size of the high-risk group, since these were to be the only men to receive individual advice. We nevertheless hoped to achieve some effect in the remaining men through a less personal, and hence less costly, approach. After the screening examination each man received a standard letter telling him that although his results were generally satisfactory heart attacks could happen to anyone, and he was urged to study the information and advice provided in a special booklet.

This advice was reinforced by posters, and, in some factories, by evening meetings, attended also by wives, for film shows, talks, question-and-answer sessions on heart disease prevention, and cookery demonstrations. At their initial examination all smokers were asked whether they would like to stop. The 40% who replied positively were sent a letter of encouragement from one of our nurses, enclosing a booklet of anti-smoking advice and a record card of daily smoking. They were asked to return the latter after three weeks, when the nurse again sent a personal letter. Short-term results were encouraging, with reductions after one year of up to 40% in the number of cigarettes reportedly smoked.

Because of a generally disappointing response to mass advice in the first two years we decided to supplement it by personal contact. Men whose coronary risk scores came closest to the high-risk level were recalled for examination at the team's annual visits and were usually seen individually by the doctor. The annual examinations, originally planned for monitoring, were also used to give personal advice, mainly on diet and smoking. In the project's third year a nurse was engaged specifically to hold anti-smoking clinics in the factories. Nevertheless, throughout the project the additional staff occupied on health education (as distinct from screening and administration) amounted to one nurse, a half-time clerical assistant, and (harder to estimate) the equivalent of about one half-time doctor; their efforts were spread among almost 10 000 men.

TABLE I—*Numbers of men examined (and response rate as % of those originally examined and still in employment)*

Follow-up year	Intervention group (n = 9734)		Control (n = 8476)	
	High-risk	Random sample	High-risk	Random sample
1	922	384 (94%)		
2	43	357 (90%)	81	614 (86%)
3	42	321 (88%)		
4	736	324 (93%)	59	538 (89%)
Final (5 or 6)	726	5373 (82%)	52	490

FOLLOW-UP

Changes in risk factor levels were assessed in the intervention group by the examination each year of a fresh 5% random sample of the men examined at entry to the study (table I). Response rates ranged from 88% to 94% of those invited (corresponding to 76% to 82% of all still in employment). The first and fourth annual examination also included all high-risk men still in employment. In the control group the same random 10% of men were invited to examination at entry, two years, and four years. The response rates at follow-up were 86% to 89% (78% to 82% of all still in employment). One control factory (GKN, Cwmbran) was closed soon after the project began, and the 449 participants were thereafter unavailable. A final examination was undertaken of all remaining employees, after five years in half of the factory pairs and after six years in the remainder. In control factories this final examination was offered to all subjects in the trial, including those men not previously approached.

Results and comment

Levels of risk-factors at each stage are shown in figs 1 and 2, based on the samples of men shown in table II (except for initial and final examinations of intervention men, where estimates were based

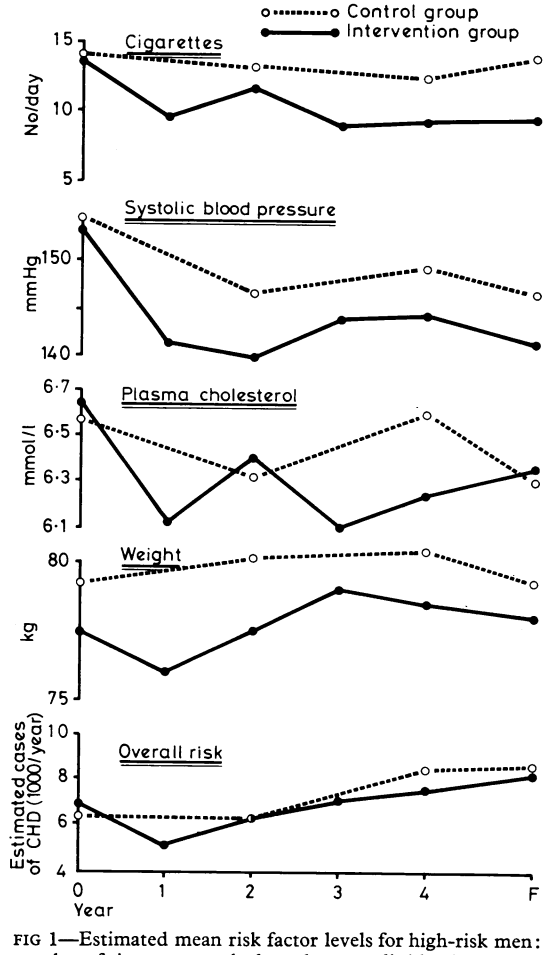

FIG 1—Estimated mean risk factor levels for high-risk men: number of cigarettes smoked per day, systolic blood pressure, plasma cholesterol concentration, body weight, and overall risk (multiple logistic function).

on all examined subjects). Table II presents a more refined analysis. In the intervention group each man's result was subtracted from his value at entry to the study to estimate his individual change for this factor (a minus sign indicating a fall). The average of these individual changes was then corrected by subtracting from it the corresponding value for the control group to allow both for any drift that might have occurred independent of our intervention and for regression towards the mean. Finally this corrected estimate of the effect of intervention was expressed as a percentage of the initial mean value for the intervention group as a whole. Statistical significance was calculated by a t test on the difference between the mean values for intervention and control samples.

The risk factor levels at entry generally showed excellent matching between the intervention and control groups. The largest disparity was for body weight in the high-risk men (fig 1), which was 1·3 kg less in the intervention group than in controls. Fortunately weight contributes little to overall risk. Overall risk was estimated by the multiple logistic method[4] applied to individuals' values for age, cigarettes smoked per day, systolic blood pressure, plasma cholesterol concentration, and body mass index. The weights (coefficients) applied to each factor were those derived from the experience of the European countries in the Seven Countries' Study (G Farchi and A Menotti, unpublished data, 1978). At entry these overall risk scores were almost identical in high-risk men but averaged 5% higher in intervention men generally.

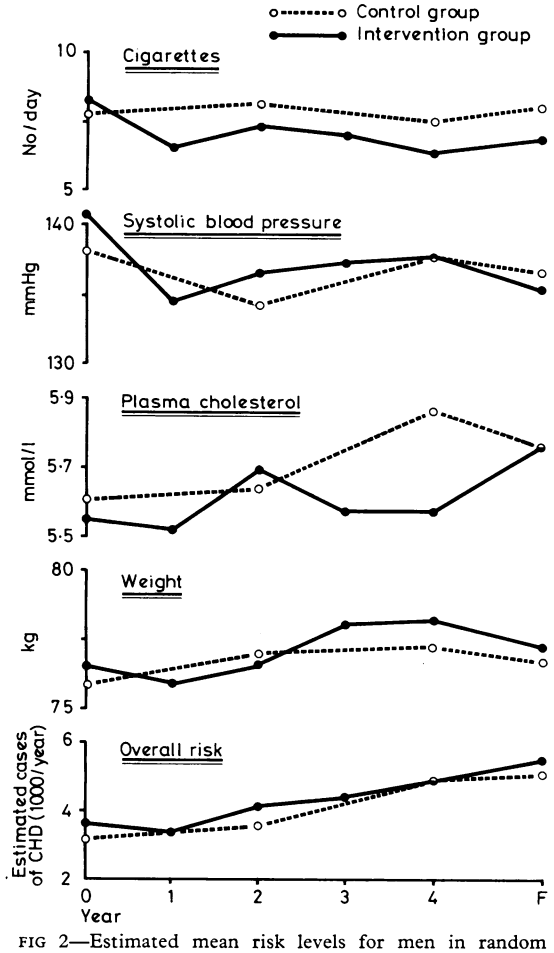

FIG 2—Estimated mean risk levels for men in random samples.

HIGH-RISK MEN

High-risk men showed the largest changes in risk factor levels. They reported a decline in mean daily cigarette consumption of 29% at the end of the first year, and this effect was sustained. The controls changed little, so that the corrected estimate for the effect of intervention at the final examination was again −29% (table II); by then 12% of those who were smokers at entry had stopped completely.

Blood pressure showed a large regression to the mean in both groups, but throughout the trial the systolic pressure averaged about 3 mm Hg lower in the intervention group. Systolic pressures of 160 mm Hg or more were recorded in 38% of the high-risk men in the intervention group initially and in 16% at final examination. An almost identical fall occurred in the control group.

Advice on cholesterol-lowering diets was more concentrated in the early months of the trial. After one year the plasma cholesterol concentration in men in the intervention group fell by an average of 8%, and 75% claimed to have changed their eating habits. Judging by the two-year results in the control group, about half this fall represented the effects of intervention. Little dietary advice was given in the second year, and the gain was lost entirely. After renewed efforts in the next two years the estimated effect of intervention was a fall of 6·9% at four years (table II). During the final stages of the trial the nurses were fully occupied with examinations, and once again most of the ground was lost.

Individual advice on weight loss was given to those high-risk men who were 15% or more overweight. By the two-year examination the high-risk group as a whole had lost 1·4 kg more than their controls. The whole of this advantage was later lost.

The estimates of overall changes in risk suggested that the benefit at the end of year 1 of about 20% had all been lost by a year later. But during the final three and a half years the net effect of intervention in these high-risk men averaged −12%, or −11% over the whole trial.

REMAINDER OF STUDY POPULATION

Results for random samples of both intervention and control groups are given in fig 2 and table II. Reported cigarette consumption was substantially reduced by intervention throughout the trial: at the final examinations the corrected estimate of change was −19% for the whole intervention group, or −16% when high-risk men were excluded. About 9% of smokers had by then been persuaded to stop (7% excluding high-risk men). Special measures to reduce blood pressure

TABLE II—*Percentage mean changes in risk factor for individuals in intervention group, corrected for corresponding changes in control group*

	High-risk men				Random sample				Random sample men (excluding high-risk)			
	Mean % change at:				Mean % change at:				Mean % change at:			
	Mean at entry (n = 1278)	2 years	4 years	Final years	Mean at entry (n = 8398)	2 years	4 years	Final years	Mean at entry (n = 7120)	2 years	4 years	Final years
Cigarettes												
% smoked	74	−10	−9	−12	51	−3	−1	−9†	47	−2	+2	−7†
No/day	14·3	−8	−19*	−29†	8·3	−12†	−15†	−19†	7·3	−14†	−10	−16†
Blood pressure (mm Hg):												
Systolic	154	−3·4	−2·1	−2·6	140	−0·4	−1·8*	−2·5†	137	+0·1	−2·2*	−2·3†
Diastolic	90	−2·1	+0·5	−1·9	84	+0·7	−2·4*	−2·2†	83	+1·1	−2·9*	−2·1†
% with systolic ≥160 mm Hg	38	−13	−5	−8	14	+9	−7	−17†	10	+20†	−40*	−16†
Plasma cholesterol (mmol/l)	6·64	−0·3	−6·9†	−0·9	5·57	+2·0*	−4·1†	+1·0	5·37	+2·4*	−3·5†	+1·7*
Weight (kg)	77·7	−1·4	−0·4	−0·4	76·5	−1·2*	+0·1	0·0	76·3	−1·2*	+0·3	−0·1
Overall risk estimate (cases of coronary heart disease/1000/year)	6·9	−5	−19*	−9	3·4	+4	−13*	−3	2·8	+7	−15†	−0·7

*Significant at 5% level, †significant at 1% level.

were confined to men with hypertension, many of whom were in the high-risk category. No obvious differences emerged.

Cholesterol-lowering dietary advice was given at first only by letters, booklets, and posters. Conversations with the men suggested that these had a considerable impact, and at each of the first two examinations about 30% of those randomly examined (excluding high-risk men) reported that they had changed their eating habits. Objective evidence of change was, however, negligible. In the middle years of the trial some effort was made to advise these men individually, the corrected estimate at four years was of a fall averaging 4% (table II). This benefit disappeared in the final stage of the trial, when the intervention effort had to be relaxed. No effects on body weight were evident at any stage, though overweight men had received postal advice in the first year.

Overall, there were no clear differences between the intervention and control groups in total risk estimates. Over the whole period of the trial, the net effect of intervention on overall risk averaged just under 4%.

Results of physical activity have not been presented, because there was no adequate measure of response, though some individuals exercised energetically and persistently. Annual questionnaires suggested a persistent modest advantage to the intervention group. Thus at four years, for example, vigorous exercise was reported by 35% of the intervention group compared with 22% of controls. This estimate of response could well be exaggerated.

EFFECT OF SCREENING IN CONTROL MEN

We did not know what effects screening might have on behaviour or use of medical care in the control group, and the assessment of changes in incidence will therefore be based on the 90% of control men who had no contact with the trial until the final examination. A comparison of risk-factor levels at the final examination between this 90% and the remaining 10% of men who had been examined before showed almost identical results for smoking, cholesterol, and weight, but a significant difference in blood pressure. The average was 4·1/2·0 mm Hg lower in the men who had been screened before. Since few had been referred for treatment, this presumably resulted from habituation to medical examinations.

Discussion

The control of coronary heart disease necessarily depends on prevention, since treatment so often comes too late. Mass medication is potentially dangerous,[5] and it would be better if risk factors could be controlled by changing habits. To be effective in middle age this would require that the risk factors did cause the disease, that the progress of the disease could be altered, and that those advised could change their habits. This report deals with the last of these issues. The answers to the first and second depend on showing changes in the incidence of disease and will form the subject of a subsequent report from the WHO European Collaborative Trial.

Screening and health education require the same rigorous evaluation as a new treatment, but this has to be organised at community level, which makes it difficult to obtain a suitable control group. The North Karelia project in Finland[6] and the Three Communities study in California[7] each used a single community as control, but this gives no estimate of the variability of results, and it is impossible to assess statistical significance. We therefore included many communities in the study and then randomised these, rather than individuals, to intervention or control status. This produced two well-balanced groups, and the controls remained free from contamination by the intervention programme proceeding elsewhere.

The measures selected for evaluation were based on the evidence available when the trial began; they would still be our choice today. More debatable was the level of resources appropriate to implementing the programme. It could be argued that a major hazard to public health merits a major investment in its control, but we had to make do largely with what was available. A bigger effort might have achieved bigger results. Periodic examination of small random samples, coupled with good response rates, provided an excellent and cheap means of monitoring progress. Despite sampling errors the overall pattern was clear. The results show the necessity of a control group to identify and allow for regression to the mean (blood pressure and cholesterol), habituation to examination procedures (blood pressure), and spontaneous changes (throughout the trial the whole study population was exposed to conflicting pressures from advertisers and health education).

It proved relatively easy to disseminate information and alter men's responses to questioning—for example, by the end of the first year 75% of high-risk men and 30% of the remainder claimed to have changed their eating habits in response to advice—but their claims were not paralleled by corresponding changes in plasma cholesterol concentrations and body weight. This was particularly evident in the men who were not at high-risk and who, during the early stages of the trial, received only letters and general propaganda. Propaganda seemed effective as a means of spreading information, but a substantial change in habits seemed to require some personal contact.

The screening examinations proved to be a two-edged weapon. In general they stimulated interest in the aims of the project, and enhanced the receptiveness to advice of the high-risk men recalled for personal consultation. The remaining men, however, tended to regard a satisfactory report as tantamount to some sort of guarantee of health, even though their letter warned that heart attacks could still happen. Only after four years, when many had recently been recalled for personal dietary advice, was there any evidence of an effect on dietary habits in the intervention group as a whole. When the intervention effort was later relaxed this benefit was soon lost.

The only strong and maintained effect of mass advice was on the number of cigarettes reported as smoked, which was persistently reduced in the intervention group. If this reduction was real this could be an important benefit, but the claims are unvalidated. Other centres in the WHO Collaborative Trial are examining the use of plasma thiocyanate levels as a means of validation.

The high-risk men responded better to advice. Their reported fall in cigarette consumption was larger, and the percentage of smokers appeared to be reduced. Average blood pressure levels were lowered by a few millimetres. The measures of the effect of dietary change on plasma cholesterol levels reflected the amount of recent personal advice, being greatest in the first year (about 3% allowing for estimated regression to the mean) and the fourth year (6·9%). Even these modest responses were quickly lost when regular personal contact could not be maintained. The same was true of weight loss. Perhaps dietary advice needs to be regarded in the same way as long-term drug treatment, with sustained consultations and encouragement over the years.

The trial has shown that coronary risk factors can be changed in the working population, given proper organisation and some supplementation of existing resources. But changes were not large, and we have not shown that they can be sustained. The participating occupational physicians concluded that on present evidence they would not recommend the general introduction of this sort of screening and health education service. At the same time they recognised incidental benefits in the form of closer contact with employees, and several individual cases were detected of men needing treatment.

If a reduction in risk factors were to be accompanied by a commensurate fall in risk then the overall coronary risk of the high-risk men was reduced by an estimated average of 11% and of the intervention group as a whole by an average of 4%. These sound small benefits, but a reduction of even 11% in the commonest cause of death would be equivalent for many other diseases to total eradication. Finally, the modest gains we have shown were achieved at modest cost. It remains to be shown what a more intensive and sustained effort might achieve.

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Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth

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Summary and conclusions

In a double-blind trial of vitamin D supplements in pregnant Asian women calciferol (ergocalciferol, 1000 IU/day) was administered to 59 women and placebo to 67 controls during the last trimester. The two groups had similar distributions of maternal age, height, parity, number of vegetarians, countries of origin, and sex and gestation of the infants.

At entry to the trial maternal serum 25-hydroxy vitamin D (25-OHD) concentrations were low in both treatment and control groups and significantly lower in vegetarians than non-vegetarians. Mothers in the treatment group gained weight faster in the last trimester than those in the control group, and at term they and their infants all had adequate plasma 25-OHD concentrations. Mothers and infants in the control group, however, had low plasma concentrations of 25-OHD and calcium and raised plasma alkaline phosphatase (bone isoenzyme) activity. Five of these infants developed symptomatic hypocalcaemia. Almost twice as many infants in the control group were small for gestational age (29% *v* 15%), but there were no significant differences between the two groups of infants in anthropometric measurements. Infants in the control group, however, had larger fontanelles, suggesting impaired ossification of the skull.

Because of the benefits to mothers and infants in the treatment group and the absence of side effects, vitamin D supplements should be given to all pregnant Asian women in the United Kingdom.

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Introduction

Despite improved living standards there is continuing clinical and biochemical evidence of vitamin D deficiency in Asian immigrants, both among children and adults.[1] This problem is not confined to Scotland and the north of England, where winter sunlight hours are short, and Turton *et al* recently showed that vitamin D deficiency occurred in pregnant Asian women in the south London district of Tooting, which contains a relatively affluent Asian community.[2]

Osteomalacia is a well-recognised complication of pregnancy in Asians living in the United Kingdom.[3] Asian women appear to be particularly at risk of vitamin D deficiency during pregnancy, since low concentrations of 25-hydroxy vitamin D (25-OHD) are found at this time.[2 4-6] Possible neonatal consequences of this deficiency include hypocalcaemia,[7] craniotabes,[6] and frank rickets.[8] Since the risks to the fetus of subclinical maternal vitamin D deficiency are not clearly defined and since birth size of Indian Asians in Britain is less than that of north Europeans and Negroes,[9 10] we have undertaken a trial, using calciferol (ergocalciferol) supplements, to investigate the effects of the vitamin on maternal and infant calcium homoeostasis and fetal growth.