

tions from other sugar phosphates, we could not deduce how much ribose-5-phosphate was actually present. However, the peak 7 integral is somewhat greater than that of β -ATP (figs 1 and 2) which is normally present in brain tissue in a concentration of 2.5–3.0 mmol/kg wet weight.¹⁶⁻¹⁹ Therefore, we believe that ribose-5-phosphate may have been present in similar concentration. A comparable large peak, also presumably attributable mainly to ribose-5-phosphate, has previously been detected by NMRS in perfused neonatal rat brain²⁰ and a rather smaller one is present in adult rabbit brain.³

Ribose-5-phosphate is an extremely versatile metabolite, which has a critical role in many biosynthetic pathways, including those for ATP and RNA. However, there has previously been no reason to suppose that ribose-5-phosphate (or any other sugar phosphate) is stored at high concentration in the brain. If our evidence is correct, and ribose-5-phosphate is indeed stored, fundamental questions are raised about brain biochemistry.

The demonstration of low PCr/P_i ratios in three infants who had had severe birth asphyxia, and the increase in this ratio during the first weeks of life indicated improvement of the metabolic energy status of brain cells. The fact that intracellular pH was no lower in these infants than in the non-asphyxiated infants was probably because the first studies with NMRS were done 42–50 h after birth. We presume that any large quantities of lactic acid produced during the asphyxia would by that time have been removed by the circulation. NMRS has previously shown that acute cerebral ischaemia in rabbits produces a profound intracellular acidosis that rapidly resolves when the cerebral circulation is restored to normal.³ The finding that mannitol infusions improved the PCr/P_i ratio in two birth-asphyxiated infants with ultrasound evidence of cerebral oedema must be treated with caution. Although the observed changes were striking, they were not maintained (table). We cannot yet conclude that mannitol has a beneficial effect on cerebral metabolism. However, these observations emphasise the potential of NMRS as a non-invasive technique for evaluating the effects of therapy in a way that has not previously been possible. The demonstration that large porencephalic cysts developed in the cerebral hemispheres of two infants some time after very abnormal ³¹P spectra had been obtained also emphasises the prognostic potential of NMRS. In one of these two infants bilateral cysts developed after birth asphyxia, but the other infant had no abnormal clinical features and a unilateral cyst developed; the most likely explanation was that this infant had had unsuspected cerebral infarction around the time of birth.

The infant with multiple congenital abnormalities including cerebral atrophy appeared to have normal ³¹P spectra, so the fundamental abnormality in this infant's brain was unlikely to be due to deranged phosphorus metabolism. In future, particularly when carbon (¹³C) NMRS of brain becomes available,²¹ it should be possible to obtain valuable information about inborn errors of cerebral metabolism.

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UK HEART DISEASE PREVENTION PROJECT: INCIDENCE AND MORTALITY RESULTS

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Summary Results are presented for the UK centre of the WHO European Collaborative Trial in the Multifactorial Prevention of Coronary Heart Disease (CHD). 18 210 men took part, aged 40 to 59; they were employed in 24 factories, which formed the allocation units for a randomised controlled trial lasting 5–6 years. Intervention comprised advice on cholesterol-lowering diet, smoking cessation, weight control, exercise, and treatment of hypertension. Advice was given mainly through factory medical departments, the staff being supplemented a little by a visiting central team. Self-reported cigarette smoking was moderately reduced, but changes in other risk factors were small and not well sustained. There was no clear effect on hard CHD end-points (coronary deaths and myocardial infarction) or on all-causes mortality. However, there was a

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36% reduction in the rate at which intervention subjects reported ill with other CHD (principally angina) during the study, and at the end fewer intervention men gave positive responses to a self-administered questionnaire on angina and chest pain. These apparent benefits were not substantiated by electrocardiographic evidence, suggesting that participation in a heart disease prevention campaign may bias reporting of symptoms. Experience in other centres of the Collaborative Trial, however, suggests that more effective risk factor control does reduce CHD incidence and mortality. This implies that for the UK the problem is to find means of enhancing the acceptance of health advice.

Introduction

How far can health education change the major coronary risk factors in a population? And how would such changes affect the mortality and incidence of coronary heart disease (CHD)? The UK Heart Disease Prevention Project¹ and the Göteborg trial² were the first randomised population-based trials set up to study these questions. Earlier trials were in unrepresentative captive populations,³⁻⁴ or had used drugs rather than a reduction in exposure to causes.⁵ Subsequently the US Multiple Risk Factor Intervention Trial⁶ and the Oslo Heart Study⁷ were set up to evaluate prevention in selected high-risk groups.

In order to increase its power, as well as to test the consistency of the findings in varied populations, the UK study was later extended to four other European countries to form the WHO European Collaborative Trial in the Multifactorial Prevention of CHD,^{8,9} with a total of 60 881 participants. From the outset the five centres were recognised as autonomous; a common protocol was adopted in order to permit both pooling of combined results and analysis of contrasts between national findings. The experience of changing risk factors has been reported already,^{10,11} and the pooled mortality and incidence results will be reported elsewhere.¹² The results from the Belgian centre, which provide an important contrast with our own, are presented in an accompanying article.

Subjects and Methods

The UK trial included 18 210 men aged 40 to 59, forming the entire eligible workforce in twenty-four factories or other occupational groups. Since health education involves a group approach, a new experimental design was followed in which the whole communities were randomised rather than individuals. Factories were arranged in pairs, matched so far as possible for size, nature of industry, and region, and in each pair one was randomly selected for the intervention programme. All male employees in the relevant age groups were invited to a screening examination which was conducted by a visiting team of specially trained nurses based at the coordinating centre at the department of epidemiology in St Mary's Hospital Medical School, London. In each factory men with the highest levels of multifactor risk (13% of the total) received more intensive advice personally from the company physician (usually 3 or 4 consultations over the next year, each lasting about 15 minutes). There was also a general programme of information and propaganda, supported by personal letters, booklets, posters, and film shows.

The staff time devoted to intervention is estimated to have been the equivalent over the whole trial, on average, of a half-time doctor and a full-time nurse, provided largely from existing staff in factory medical departments.

The interventions were: (1) *cholesterol-lowering dietary advice* to all men, based mainly on reducing saturated fat intake and cholesterol, with encouragement to prefer oils and soft margarines to hard fats; (2) *cessation of smoking*; (3) *weight reduction*, for those 15% +

overweight; (4) *exercise* (a daily brisk walk or callisthenics) for the sedentary; (5) *control of hypertension* for those with mean systolic pressure of 160 mm Hg or above, usually in the first instance by 'Neo-NaClex-K' (bendrofluzide 2.5 mg + potassium) 1-2 tablets daily.

Changes in risk factors were monitored by reexamination of random samples (a fresh 5% annually in intervention factories and the same 10% biennially in controls). The 10% of control men called for screening were excluded from incidence and mortality calculations, in case the examinations had altered their behaviour or treatment. All men in employment at the start of the trial formed the population at risk for mortality rates, excluding only those men (<1%) who could not be identified and therefore "tagged" in the National Health Service Central Registry which sent copies of death certificates of all those who died. Thus mortality follow-up should be complete and unbiased. Morbidity recording was based on notification by factories, supplemented by a periodic systematic search (or "audit") of personnel records at the place of work, to identify leavers and discover all absences lasting three weeks or longer. Further inquiries to general practitioners and hospitals were undertaken, wherever a cardiovascular cause was suspected or could not be excluded.

The full evidence in each suspected case of cardiovascular disease, fatal or non-fatal, was reviewed by one of us (HT-P), without knowledge of the subject's intervention/control status, and classified by WHO Registry criteria.¹³ The primary end-point groupings were:

1. Fatal CHD (myocardial infarction + other sudden death, presumed CHD)
2. Fatal CHD + non-fatal myocardial infarction
3. All deaths

A record was also made of:

4. Other CHD (including angina)
5. Fatal and non-fatal strokes

Incidence estimates for non-fatal events are based on men remaining in employment: attempts to follow up the leavers would have introduced bias, since it was easier to trace intervention subjects (90% of control men had had no personal contact with us). Combined rates for mortality plus morbidity are based on the whole study population at entry.

The trial ended after 5 years in half the factory pairs and after 6 years in the others. All continuing employees were invited for examination in order to assess differences in (1) risk factors, and (2) prevalence of symptoms of CHD and electrocardiographic abnormalities. ECGs were coded independently in duplicate, without knowledge of intervention/control status. Incidence results reported here are for the period up to the final audit of illnesses, deaths, and leavers which preceded the final examinations in each factory.

Owing to the allocation of clusters rather than individuals, the usual methods for calculating confidence intervals and significance are not appropriate. Instead, intervention effect was estimated from the difference in rates within each factory pair. To take account of variations in factory size each such difference was then weighted by the inverse of its variance, the weighted differences being combined to derive a normally distributed statistic. (The statistical aspects of cluster allocation will form the subject of a separate report.)

Results

At entry the two sides of the trial were well balanced with respect to major risk characteristics.^{9,10} One control factory closed soon afterwards; mortality follow-up was unaffected but there was no morbidity follow-up.

Table 1 presents the net changes in intervention factors, averaged over the whole trial. All changes are in the predicted direction; but, except for self-reported cigarette consumption, they are small. The impact on smoking increased progressively through the trial, but with other factors there was difficulty in sustaining a response. Thus at the 4-year point, when dietary efforts had been greatest, the

TABLE I—ENTRY VALUES AND MEAN NET CHANGES IN RISK FACTORS AND MULTIPLE LOGISTIC FUNCTION IN INTERVENTION MEN

	All men (n=9734)		High risk group (n=1278)	
	Entry	Net change %	Entry	Net change %
Plasma cholesterol	5.57 mmol/l	-0.4	6.64 mmol/l	-2.7
Cigarettes	11.3/day	-16	14.3/day	-19
% Cigarette smokers	51%	-4	74%	-10
Weight	76.5 kg	-0.4	77.7 kg	-0.7
Systolic blood-pressure	140 mm Hg	-1.6	154 mm Hg	-2.7
Combined MLF (CHD/1000/yr)	3.4	-4	6.9	-11

net average reduction of plasma cholesterol was 4.1%, yet 1-2 years later this advantage had quite disappeared. High-risk men received personal advice and they showed correspondingly larger net changes.

For each man at each examination a multiple logistic estimate of CHD risk was calculated, based on the intervention risk factors.⁹ The changes in this function summarise the overall impact of intervention on risk factor levels. For the intervention group as a whole the net reduction averaged 4% (13% at 4 years), and for high-risk men it was 11% (19% at 4 years). These changes were smaller than expected, implying that a trial of this size would be unlikely to identify a significant effect on incidence.

In contrast to these small changes in the objective tests, questionnaires (and conversations with the men) gave the impression of extensive modification of habits: at the end of the first year, for example, 75% of high-risk men and 30% of the others claimed to be eating differently as a result of advice received and large differences in self-reported behaviour were also found at final screening.¹⁴

Table II shows annual cumulative rates for the main end-points, calculated by the life-table method. For fatal CHD the first year saw an apparent doubling of the rate in the intervention group, largely due to exceptionally low rates in two large control factories; thereafter the gap narrowed. Non-fatal myocardial infarction was initially more frequent in the control group; when combined with fatal CHD the rates were

TABLE III—PREVALENCE AT FINAL EXAMINATION OF ANGINA, HISTORY OF SEVERE CHEST PAIN; ECG EVIDENCE OF INFARCTION, OR ANY ISCHAEMIA

	Prevalence %		
	Control (n=4912)	Intervention (n=5670)	
Angina	6.70	4.90	p<0.01
History of severe pain	8.55	7.09	p<0.05
ECG: infarction*	1.33	1.38	NS
any ischaemia†	9.65	10.12	NS

*Minnesota codes 1.1-2. †Minnesota codes 1.1-3 or 4.1-3 or 5.1-3 or 7.1.

in approximate balance. The combined rate was lower in the intervention member in seven of the twelve factory pairs.

The category of "other CHD" (principally new angina) showed a large and significant advantage to the intervention group—a 50% reduction in the first year, and 36% overall. For "total CHD" this gives a final advantage of 4% to the intervention group. Procedures and results were reviewed carefully for any overt evidence of bias in these softer end-points but none was found, suggesting that the differences did arise with the men and their general practitioners and not within our monitoring system.

The number of strokes was rather small to assess the effect of the antihypertensive measures, as can be seen by the annual fluctuations. There was no significant difference. By the third year 3.2% of the intervention group were on antihypertensive drugs, but, among these middle-aged working men, diagnosed CHD outnumbered strokes by approximately 12:1.

In case of possible adverse effects of intervention a watch was kept on cancer deaths. No overall effect was apparent. All-causes mortality during the first year was 78% higher in the intervention group, most of this excess being due to CHD (as described above). By the end of the trial the cumulative excess was down to 11%. For both all-causes and cancer mortality half of the factory pairs recorded a higher rate in the intervention member and half did not.

Table III presents prevalence rates at the final examinations

TABLE II—YEARLY CUMULATIVE EVENT RATES, PERCENT (LIFE-TABLE METHOD), AND PERCENTAGE NET DIFFERENCE BETWEEN INTERVENTION AND CONTROL: NUMBERS OF EVENTS IN PARENTHESES*

Yr	Group (control n=7617; intervention n=9734)	Fatal CHD (302 cases)	Fatal CHD + not-fatal MI (707 cases)	Other CHD (223 cases)	Strokes, fatal + non-fatal (79 cases)	Cancer deaths (194 cases)	All deaths (684 cases)
1	Control	0.12 (9)	0.71 (54)	0.30 (21)	0.08 (6)	0.09 (7)	0.32 (24)
	Intervention	0.24 (23)	0.74 (72)	0.15 (14)	0.09 (9)	0.16 (16)	0.57 (55)
	Δ	+100%	+4%	-50%	+13%	+78%	+78%
2	Control	0.41 (22)	1.49 (59)	0.66 (25)	0.16 (16)	0.36 (20)	1.00 (52)
	Intervention	0.51 (26)	1.45 (69)	0.32 (16)	0.18 (8)	0.33 (16)	1.25 (67)
	Δ	+24%	-3%	-52%	+13%	-8%	+25%
3	Control	0.74 (25)	2.21 (55)	1.03 (24)	0.28 (9)	0.51 (12)	1.71 (54)
	Intervention	0.86 (34)	2.20 (72)	0.50 (16)	0.27 (9)	0.57 (23)	2.01 (74)
	Δ	+16%	-0.5%	-51%	-4%	+12%	+18%
4	Control	1.20 (35)	3.04 (62)	1.39 (22)	0.43 (11)	0.69 (13)	2.48 (59)
	Intervention	1.27 (40)	3.10 (86)	0.81 (25)	0.33 (6)	0.81 (23)	2.89 (85)
	Δ	+6%	+2%	-42%	-23%	+17%	+17%
5*	Control	1.62 (28)	3.82 (52)	1.84 (23)	0.47 (3)	0.99 (20)	3.41 (63)
	Intervention	1.63 (31)	3.90 (70)	1.04 (17)	0.46 (11)	1.04 (20)	3.75 (79)
	Δ	+1%	+2%	-43%	-2%	+5%	+10%
6*	Control	1.91 (10)	4.44 (22)	2.14 (8)	0.47 (0)	1.31 (11)	4.25 (30)
	Intervention	2.07 (19)	4.69 (34)	1.38 (12)	0.48 (1)	1.35 (13)	4.71 (42)
	Δ (SE)	+8%	+6%	-36%	+2%	+3%	+11%

*Denominators have been adjusted for factories not completing follow-up exactly at anniversary.

of angina and history of severe central chest pain (elicited by standard self-completed questionnaire), and of electrocardiographic evidence of myocardial infarction or ischaemia. The prevalence of angina is 27% lower and of severe chest pain 17% lower in the intervention men, consistent with the reporting of illness episodes. However the prevalence of positive electrocardiographic findings is 4–5% higher than in controls.

Discussion

The programme of medical examinations and preventive advice was popular, reflecting a widespread concern among men (and their wives) at risk of a heart attack. Response rates were high, and the project promoted good relations between employees and medical departments. It was relatively easy to disseminate information on heart disease and to alter men's responses to questionnaires, most men claiming to have made some change as a result of our advice; but, unfortunately, objective testing showed that these changes were generally small. Such success as was achieved seemed to depend on continued personal contact and encouragement.

Larger changes in risk factors were obtained in other centres of the WHO Collaborative Trial, amounting in Belgium to an overall net reduction of 16% in estimated coronary risk,¹⁵ compared with 4% in the UK centre. Maybe this reflects a particular reluctance of British men to alter their behaviour for health reasons, or perhaps it was due to the small number of additional staff employed to give advice. Only in regard to self-reported smoking reduction was the UK centre more successful than others, this factor having long been stressed by British doctors. In contrast the message on diet and cholesterol reduction has been weak and confused, and here our centre was the least successful.

With such a small overall impact on risk factors there was little chance of identifying an effect on incidence. The trend was weak and adverse for fatal CHD, and weak but favourable for non-fatal myocardial infarction. For "other CHD" (principally new angina), which was not a primary end-point, the trend was strongly favourable. Our initial concern that this arose from an undetected bias within our illness-monitoring system is allayed by the final screening questionnaire on symptoms, which is consistent; but not by the electrocardiographic evidence. These results suggest that either intervention prevented cardiac pain alone of CHD manifestations, which seems unlikely, or that it tended to alter responses to it, even to the extent of some denial. This paradoxical mechanism of apparent disease prevention reinforces the necessity for objective end-point criteria.

Safety must be a major concern of any preventive effort. Four previous trials related to CHD prevention have reported unexpected adverse effects on mortality. The Los Angeles Veterans Study,³ a trial of a diet high in polyunsaturates, observed some excess of early deaths from cancer, which was not confirmed in other trials of a similar diet.¹⁶ The WHO Clofibrate Trial⁵ found a large excess of deaths from an assortment of non-cardiovascular causes; this did not seem to be related to reduction of serum cholesterol levels and it may have been due to some other action of clofibrate. The Whitehall Study's trial of smoking cessation¹⁷ reported an excess of non-lung cancers in the intervention group. The US Multiple Risk Factor Intervention Trial⁶ noted an excess of cardiac deaths in subjects with hypertension and electrocardiographic abnormalities, most of whom had received high doses of diuretics. These results justify concern over the chronic toxicity of drugs in primary

prevention,¹⁸ but they also at least raise the question of possible deleterious effects from other abrupt changes in biological equilibrium: if the body has some capacity to adapt to an adverse exposure, then perhaps sudden reduction in that exposure might lead to a period of disequilibrium.

In the intervention group of the present trial there was a considerable reduction in exposure to cigarettes, an increased intake of polyunsaturates, and an increase in drug treatment of hypertensives. It was therefore with some anxiety that we observed in the first year of the trial a net excess of 100% in CHD deaths and of two-thirds in deaths from other causes. However, this excess was not consistent across factory pairs, it was not cause-specific, and it did not subsequently increase. It may have been due to the low death rates in the control factories in the first year which doubled in the next year. In retrospect a running-in period of morbidity and mortality recording before initiating intervention might have been useful. Although the early mortality excess in the intervention group may have occurred by chance and was not observed in the other collaborating centres, it remains a cause for concern.

Conclusion

This study has shown that in the UK our attempts to reduce coronary risk factors through occupational medical services met with only limited success. Perhaps the public is now more receptive to such advice than when this trial started a decade ago; possibly with more or different staffing the impact might have been greater. To answer these questions new demonstration projects are required, employing a wider variety of approaches. Without such information more effective services cannot be planned.

With an average net reduction of only 4% in overall CHD risk this section of the WHO Collaborative Trial has not contributed useful evidence on the reversibility of the risk of heart attack. Fortunately other sections of the trial achieved larger changes in risk factors,¹¹ and they have observed approximately corresponding reductions in CHD incidence and mortality.¹² The Belgian results¹⁵ provide evidence of benefit supporting that from the Oslo Heart Study.⁷ The implication for public health policy in the UK is that a preventive programme such as we evaluated in this trial is probably effective, to the extent that it is accepted; the problem is how to improve its acceptance.

We again thank supporting staff, the participating occupational physicians, and their companies.¹⁰ The computing was undertaken by Mrs Sheila Woods and Miss Christine Rees. The cost of the study was borne by the Department of Health and Social Security, and 'Neo-NaClex-K' was kindly supplied by Glaxo Ltd. The UK Heart Disease Prevention Project was based in the Epidemiology Department of St Mary's Hospital Medical School, London.

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BELGIAN HEART DISEASE PREVENTION PROJECT: INCIDENCE AND MORTALITY RESULTS

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Summary Results are presented from the Belgian Heart Disease Prevention Project, part of the WHO European Collaborative Trial in the Multifactorial Prevention of Coronary Heart Disease (CHD). 19 409 men aged 40–59 yr took part; they were employed in thirty factories which formed the allocation units for a randomised controlled trial lasting 5–6 yr. The intervention package consisted largely of health education promoting a cholesterol-lowering diet, smoking cessation, weight control, physical activity, and treatment of arterial hypertension. A programme of information was supplemented by face-to-face counselling at the workplace by two physicians attached to the project. The coronary risk profile was reduced in the intervention group, compared with that in the control group, especially during the first 4 yr, by effects on serum cholesterol, number of cigarettes smoked daily, and arterial blood-pressure. Total mortality was 17·5% lower in the intervention group than in the control group ($p=0\cdot038$). Coronary mortality was reduced by a non-significant 20·8% whereas CHD incidence (non-fatal myocardial infarction plus fatal myocardial infarction plus sudden deaths) was reduced by 24·5% ($p=0\cdot031$). Non-fatal myocardial infarction (not a major end-point) was similarly reduced by 26·1% ($p=0\cdot030$).

Introduction

By the 1950s and 1960s it was clear that many causal factors must be involved in the coronary heart disease (CHD) epidemic affecting most of the industrialised countries.

Hence, primary prevention of CHD seemed to call for simultaneous attack on several major risk factors. In 1971 the World Health Organisation convened an international meeting where different strategies were proposed. Randomised trials in selected high-risk groups were advocated by an American and Norwegian group: they resulted, respectively, in the Multiple Risk Factor Intervention Trial¹ and the Oslo Study.² While the former was directed at trying to modify high serum cholesterol, high blood-pressure, and cigarette smoking, the latter was a bifactorial trial acting on high serum cholesterol and cigarette smoking. A community-wide approach was proposed by groups in Sweden³ and Finland;⁴ the Swedish trial was both controlled and randomised but the Finnish one was only controlled, owing to local demand for intervention in the high CHD area of North Karelia.

A UK group, led by Prof G. Rose, proposed a multifactorial trial in industry.⁵ This approach was the most appealing for a Belgian inter-university group from the universities of Ghent and Brussels. Together with groups from Poland, Italy, and later Spain, they joined the UK group for what was to be called the WHO European Collaborative Group.⁶ Preliminary incidence results from the European Collaborative Group have been published (*Europ Heart J* 1983; 4: 141–47). The two largest collaborating centres are Belgium and the UK, and the UK results are reported in the accompanying paper.

Subjects and Methods

The Belgian Heart Disease Prevention Project (BHDPP) has been described previously.^{7–9} It conforms broadly to the international protocol elaborated by the WHO Collaborative Group and described in the UK report.¹⁰ Hence, we shall confine ourselves to some of the special features of the Belgian programme. Fifteen pairs of factories were randomised with a total of 19 409 males aged 40–59 yr at entry.

Screening procedures conform largely to the international protocol.⁶ 21% of the intervention subjects (1601) were designated "high-risk". All subjects had an electrocardiogram at rest, so CHD incidence in both the intervention and control groups can be related to baseline ECG features. The overall participation rate was 83·7%.

Intervention procedures broadly conform to the international protocol.⁶ Physicians in charge of face-to-face counselling were part of the team and moved according to a planned schedule from one factory to another. High-risk subjects were invited for preventive counselling three times during the first year, twice in the second, and yearly thereafter. Besides the 5% random sample invited yearly, a non-random 5% of the lower-risk group, different on each occasion, was invited for individual counselling. Since only half the defined hypertensive subjects (systolic pressure ≥ 160 mm Hg, average of four readings) were in the high-risk group the other half were invited during the first year for advice concerning their hypertension and were referred to their general practitioner for drug treatment; drug treatment could not be undertaken by programme physicians or factory physicians. In several factories with canteens serving hot meals, a dietician* evaluated nutritional habits and advised the chef on reduction of total calories, saturated fats, and cholesterol.

Final screening.—All subjects at work were invited to a final screening and 71% accepted. In a random sample of the intervention and control groups serum thiocyanate was assessed.

Follow-up.—Mortality follow-up was complete except in 54 subjects (30 intervention and 24 control), for whom vital status at the end was not known (thus follow-up was 99·7% complete).

GEOFFREY ROSE AND OTHERS: REFERENCES—continued

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