

controlled trials offer a solution to this problem, because they test a smoking cessation intervention in the most rigorous way possible using human subjects (2, 37, 70). However, even in such trials, those assigned to the no-intervention group modify their smoking habits, and those assigned to the intervention group have incomplete success in quitting.

Ideally, each risk factor should be treated independently, but modification of one risk factor often results in changes in other risk factors. For instance, some studies have noted that cigarette smoking cessation can lead to a modest weight gain (3, 26, 47). In a good primary prevention program there would be an effort to reduce or to eliminate the weight gain that sometimes accompanies cessation. Although the multifactorial approach is less precise, it has been considered to be a more practical approach to the problem. There has been only one trial of smoking cessation per se (50, 51).

Two types of primary prevention trials involving smoking cessation are underway. The first type of study, exemplified by the Multiple Risk Factor Intervention Trial (MRFIT), selected subjects at high risk of CHD based on a combination of cigarette smoking history, elevated blood pressure, and high serum cholesterol level (43). Subjects were then randomized into either a special treatment group or a comparison group. The Whitehall study (50, 51) and the Oslo study (27) are also of this type.

In the second type of study, communities or groups rather than individuals are randomized into a treatment or a control group. The WHO heart disease study randomized men according to the factory where they work and followed the individual factory workers (70). The North Karelia study randomized two separate communities in Finland (48). Whereas the factory workers were individually followed, the communities were monitored only in a cross-sectional manner and individuals were not followed longitudinally.

The primary hypothesis in these studies is that reduction of the risk factors will reduce the incidence of and mortality from CHD. The first step in testing this hypothesis requires that the subjects or groups be successfully recruited and categorized at entry to the study and that a very high percentage be successfully followed for the duration of the study.

The second step in testing the hypothesis requires the successful reduction of the major risk factors—smoking, high blood pressure, and high serum cholesterol. Often a selected subsample of high risk subjects receives more intensive individual intervention, but the rest of the treatment group receives only community health education. It is not known how large a reduction in risk factors is necessary to observe a decrease in CHD, except that the larger the reduction in risk factor the greater the chance for a decrease in CHD. Specific goals for reduction of risk factors can be based on the presumption

that such reduction would result in a statistically significant decrease in the incidence of and mortality from CHD according to the observational epidemiologic studies. The relationship between the reduction of this risk score and actual reduction in the frequency of disease is, of course, the hypothesis being tested.

The third and most critical step depends on the first two: that is, the measurement of outcome—changes in the incidence of or death from CHD. The ability to measure the incidence requires careful and unbiased monitoring of the sample. The determination of total and cardiovascular mortality is much simpler, since it depends only on minimizing the number of participants lost to followup. The community studies attempt to compare the death rates between two or more communities, and the power of such a statistical test is obviously very weak.

Both the community studies and the individualized studies are also confounded by the uncertainty of the interval between risk factor change and reduction in risk of disease. Those subjects most likely to die or to have a heart attack in the first few years of the study are those with the most extensive disease at baseline. Unless the population is followed long enough to include both the lag period and the effects of the initial selection of those with advanced subclinical disease, a spurious interpretation of the study results is possible.

Generally, studies of experimental communitywide interventions are unlikely to determine the efficacy of smoking cessation on reducing the incidence of and mortality from CHD because of the difficulty in determining the effects of smoking cessation on specific individuals in the community and in separating out the effect of smoking cessation from other changes in the community. In many of these studies the percentage of men who reported quitting smoking is relatively small, which reduces the power of the study at least in terms of smoking cessation.

This review focuses on all intervention studies involving smoking cessation for which CHD mortality outcome data have been published. In another section of this Report a detailed review on smoking cessation in clinical and community trials is presented. Discussed in detail here are data from the U.S. Multiple Risk Factor Intervention Trial (43), the Whitehall study in London, England (51), the Oslo study in Norway (27), the WHO European Collaborative study (69), and the North Karelia project in Finland (48). Omitted from this section are smoking intervention studies without published mortality outcome data, such as the Stanford, California, three-community study (16), the Stanford five-community study (15), the Göteborg, Sweden, study (64, 65, 66), and the Helsinki, Finland, study (46).

Essential details from each trial are described in the following pages and tables. The initial population characteristics and risk factor changes are summarized in Table 4. The mortality outcomes in the intervention and control groups are summarized in Table 5 for coronary heart disease and total mortality. Available results are also given for other circulatory diseases, lung cancer, and other cancer. The results for the four trials involving cohort mortality followup are combined in Table 6. Coronary heart disease incidence rates from the Oslo and WHO studies are presented in Table 7. A comparison of death rates in the MRFIT intervention and control groups as a function of initial smoking status and status at 1-year followup is summarized in Table 8. Observed deaths in the MRFIT and Whitehall studies are compared with expected deaths based on general population rates in Table 9. Comparisons of reductions in CHD and total mortality from the observational studies and from the MRFIT and Whitehall studies are made in Table 10.

Randomized Controlled Trials of Individuals

Multiple Risk Factor Intervention Trial

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized controlled trial to investigate the effect of reducing cardiovascular risk factors in a group of asymptomatic men at high risk of cardiovascular disease (43). Out of 361,662 men initially screened, 12,866 men aged 35 to 57 were selected for the trial because they were at increased risk of death from CHD, but without clinical evidence of CHD, and agreed to be randomized and reexamined. A series of three complex screening procedures were used to select the final 12,866 men, who constituted only 3.6 percent of those screened. Men were designated as at increased risk because their levels of three risk factors—cigarette smoking, serum cholesterol, and blood pressure (BP)—were sufficiently high at a screening visit. All of these men were in the upper 15 percent of a risk score distribution based on data from the Framingham heart study; about two-thirds were in the upper 10 percent of risk. For example, a man whose diastolic BP was 90 mm Hg and who reported smoking 30 cigarettes per day was risk eligible at the 10 percent level if his serum cholesterol level was at least 295 mg/dl. The study was restricted to men, since including women, with their substantially lower risk of CHD, would have necessitated a larger study population.

The men were randomized into two groups of equal size and identical baseline characteristics from December 1973 through February 1976. A special intervention (SI) group of 6,428 men received an intensive counseling program, aimed at cessation of cigarette smoking, weight loss, and a change of diet for a reduction of elevated serum cholesterol and BP levels. A usual care (UC) group of

TABLE 4.—Basic description of smoking cessation intervention studies of males, including demographic characteristics and risk factor changes

Variable	Individual intervention			Factory intervention	Community intervention	
	MRFTT	Whitehall	Oslo	WHO	North Karelia	
					1972	1977
Number in intervention (I) group	6428	714	604	24,615	1834	1785
Number in control (C) group	6438	731	628	25,169	2665	2616
Mean age (yrs)	46.2	52.9	45.2	48.5	~42	~47
Age range (yrs)	35-57	40-59	40-49	40-49	25-59	30-64
Race (% white)	90	~100	~100	~100	~100	
Followup period: Start date	12/1973	1968-70	1972-73	1971-76	1972	
End date	2/1982	1979	1978	1982	1977	
Average length (yrs)	7	10	5	6	5	
Risk factor (RF) at start						
Cigarette smokers (%)	59	100	79.4	60	51.5	
Relative change ¹ /end	-29%	-24%	-12%	-3.4% ²	-2.5%	
Relative change/whole period	-31%	-54%	-16%	-1.9%	- ³	
Average no./day cigarettes	20	19.3	12.7	11.2	9.4	
Relative change/end	-30% ²	-33%	-37%	-10.1%	-9.8%	
Relative change/whole period	-30% ²	-53%	-45%	-8.9%	-	
Serum cholesterol (mg/dl)	254	213 ⁴	329	217	263	
Relative change/end	-2%	-	-12%	-0.5%	-4.1%	
Relative change/whole period	-2%	-	-13%	-1.2%	-	
Blood pressure ⁵ (mm Hg)	91	- ⁴	- ⁴	138	91.5	
Relative change/end	-4%	-	-	-2.0%	-2.8%	
Relative change/whole period	-4%	-	-	-2.0%	-	
Combined change in CHD risk	-22.2%	-	-	-11.1%	-17.4%	

¹ Relative change = $(RF_I - RF_C)/RF_C$, except for North Karelia, where relative difference is determined from (I-C) 1977 and (I-C) 1972.

² Estimated from available data.

³ Not measured or not reported.

⁴ Risk factor is not part of intervention.

⁵ Diastolic, except for systolic in WHO study.

6,438 men received annual checkups including medical history, physical examination, and laboratory studies at the MRFTT clinics, but were referred to their personal physicians or other community medical facilities for such treatment of their risk factors as was considered individually appropriate. Thus, no intervention program was offered to them. The results of their screening and annual examinations were provided to their respective physicians who were also informed as to the scientific objectives of the study.

The smoking intervention urged those SI participants who smoked cigarettes to quit, but no effort was made to alter the smoking habits of those who smoked only pipes and cigars (29). Dosage reduction—

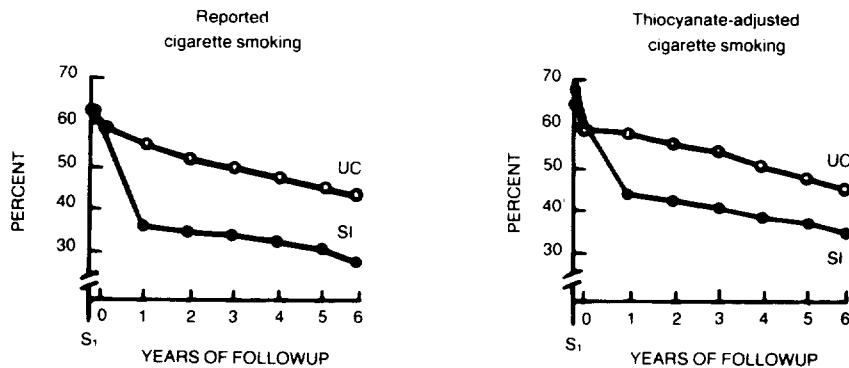


FIGURE 1.—Mean risk factor levels for cigarette smoking by year of followup for Multiple Risk Factor Intervention Trial Research Group participants

NOTE: SI indicates special intervention

UC indicates usual care

S₁ indicates first screening visit

SOURCE: Multiple Risk Factor Intervention Trial Research Group (43).

switching to cigarettes low in tar and nicotine—was recommended only as an intermediate step to cessation. Conventional behavior modification techniques were used throughout the trial; aversive techniques and hypnosis were used in selected instances. Ten-week group sessions at the beginning of the trial and 5-day quit clinics during the final years were found to be particularly successful intervention approaches. Further details on the smoking intervention are provided in an earlier section of this Report, and the serum cholesterol and BP interventions are described elsewhere (43).

Statistically significant CHD risk factor reductions between the SI and UC groups were obtained at each annual visit. Of particular interest was the reduction in number of cigarette smokers, as shown in Figure 1. At the beginning of followup, 59 percent of all men had reported themselves as current cigarette smokers. At the 12-month followup, the stated quit rates were 43 percent for SI men and 14 percent for UC men; at 72 months, the rates were 50 percent and 29 percent, respectively. Serum thiocyanate-adjusted quit rates at 12 months were 31 percent for SI men and 12 percent for UC men; at 72 months they were 46 percent and 29 percent, respectively. This means that the SI group reduced its level of smokers 30 percent more than the UC group. The risk factor changes are summarized in Table 4.

As of February 28, 1982, after an average period of followup of 7 years, there were 260 deaths among the UC men, of which 124 were ascribed to CHD and 21 to other cardiovascular causes, as summa-

rized in Table 5. There were 265 deaths among the SI men, of which 115 were ascribed to CHD and 23 to other cardiovascular causes. The key mortality endpoint of CHD was 7.1 percent less in the SI group than in the UC group, while the death rate for all causes was 2.1 percent higher for the SI men. The approximate 90 percent confidence interval (CI) for the percentage change in CHD mortality attributable to MRFIT intervention ranges from a 25 percent decrease to a 15 percent increase. There were 34 lung cancer deaths in the SI group and 28 in the UC group and 47 other cancer deaths in the SI group and 41 in the UC group.

The number of deaths in the UC group was substantially short of expectation for the 6 complete years of followup as well as for the average followup period of 7 years, as shown in Table 9. These mortality patterns appear to be similar to those seen in healthy persons selected for life insurance policies (22, 41). On the basis of the design risk factor change assumptions and the Framingham risk functions, 442 deaths (including 187 from CHD) were expected among the 6,438 UC men by the end of 6 years of followup, but only 219 (including 104 from CHD) occurred (50 percent of expected); about 515 deaths (including 220 from CHD) were expected after 7 years, but only 260 deaths (including 124 from CHD) occurred.

At least three possible explanations for these results must be considered: (1) such an intervention program is without benefit in terms of substantial decreases in mortality; (2) the intervention program does affect CHD mortality, but the benefit was not observed in this study, an effect of chance; or (3) one or more constituents in the intervention program may have had an unfavorable effect on survival in some subgroups, offsetting the beneficial effects of others.

Of these possible interpretations, a combination of favorable and unfavorable effects of the intervention program seems most plausible to the MRFIT investigators. Even with the unexpected sizable risk factor reduction among the UC men, the lower-than-expected UC mortality, and the duration of intervention averaging only 7 years, the likelihood that these factors resulted in missing an overall positive effect is relatively low. The data suggest that except for some groups of hypertensive persons, particularly those with resting ECG abnormalities, the MRFIT intervention is apparently associated with a lower CHD mortality in the SI group.

The MRFIT data also warrant analysis as an observational study (Table 8). Of those who had been cigarette smokers at entry, 1,365 reported quitting at year 1 interview (and had confirmatory blood SCN levels) and 6,298 did not quit. Over an average 6 years of further followup, those who quit smoking at year 1 had a 1.10 percent CHD mortality rate, while those who continued smoking had a CHD mortality rate of 2.03 percent. This corresponds to a relative risk of 0.54 (1.10/2.03) or a 46 percent lower risk of CHD death for

TABLE 5.—Comparison of deaths (d) and death rates (r) in the intervention and control groups of four randomized controlled trials

Cause of death	Intervention group		Control group		Percentage difference ^a (r _i -r _c)/r _c
	r ¹	d _i ¹	r _c ¹	d _c ¹	
MRFIT: 7-year deaths					
Coronary heart disease	.0179	115	.0193	124	-7.1
Other circulatory disease	.0036	23	.0033	21	+9.8
Lung cancer	.0053	34	.0043	28	+21.6
Other cancer	.0073	47	.0064	41	+14.8
All other causes	.0072	46	.0071	46	+0.1
All causes	.0412	265	.0404	260	+2.1
Whitehall: 10-year deaths					
Coronary heart disease	.0696	49	.0848	62	-19.1
Other circulatory disease	.0182	13	.0164	12	+11.0
Lung cancer	.0252	18	.0328	24	-23.2
Other cancer	.0392	28	.0164	12	+139.0 (p=.01)
All other causes	.0210	15	.0246	18	-14.6
All causes	.1723	123	.1751	128	-1.6
Oslo: 5-year deaths					
Coronary heart disease (Fatal MI and sudden coronary death)	.0099	6	.0222	14	-55.4
Other circulatory disease	.0033	2	.0016	1	+106.3
All cancer	.0083	5	.0127	8	-34.6
All other causes	.0050	3	.0016	1	+212.5
All causes	.0265	16	.0382	24	-30.6
WHO: 6-year deaths					
Coronary heart disease	.0150	367	.0162	355	-7.4
All other causes	.0254	630	.0253	569	+0.4
All causes	.0404	997	.0415	924	-2.7

¹ Death rate (r) equals deaths (d) divided by initial number in group.

^a Unless indicated with a p value, differences are not statistically significant (p > 0.05), based on a two-tailed test for a Poisson variable.

those who quit smoking compared with those who continued. For all-cause mortality, the relative risk was 0.73 or a 27 percent lower risk for those who quit compared with those who continued to smoke.

As demonstrated in subsequent portions of Table 8, when these subjects are analyzed according to level of smoking at entry or by status in the SI or the UC group, those who quit smoking always enjoyed a substantially more favorable survival rate than those who didn't quit.

Thus, MRFIT data are entirely consistent with the numerous previous studies showing that those who quit cigarette smoking enjoy a substantially improved survival.

In conclusion, the MRFIT study has shown that it is possible to apply an intensive long-term intervention program against three

coronary risk factors with considerable success in risk factor changes. These results are accompanied by an apparent heterogeneity of effects among sizable subgroups, and there must be caution in reaching conclusions from such subgroup data. It may be relevant that multifactor intervention received a less than optimal test, owing in part to unexpected declines in risk factor levels and in part to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a "treated" group.

Whitehall Civil Servants Study

A randomized controlled trial was set up to provide an unbiased estimate of the consequences of smoking cessation in middle-aged men (50, 51). A total of 1,445 male cigarette smokers with an especially high cardiorespiratory risk were selected from 16,016 men aged 40 to 59 who had undergone a cardiorespiratory screening examination in the Whitehall study of male civil servants in London. Using a modification of the multivariate linear discriminant function coefficients that were calculated for predicting coronary heart disease (CHD) among the Framingham men aged 30 to 62, a risk score was similarly calculated for each man who smoked five or more cigarettes a day. This score ranked the smokers according to their estimated risk of major illness or death from cardiorespiratory disease. The distribution of the score was tested early in the study, and a cutoff point was determined such that the scores of 10 percent of all men and 32 percent of smokers were eligible and exceeded this value, which was thereafter used to define eligibility for the trial.

Men receiving medical care for heart disease or elevated blood pressure, those found to have either severe hypertension or diabetes mellitus, and those with major concomitant disease were excluded from the trial. Additionally, all men taking psychotropic drugs or with a record of previous psychiatric inpatient treatment were eliminated. If during the 1-year interval between initial screening and trial interview they had died, moved away, or stopped smoking, they were then not eligible for the study. The remaining 1,445 high risk eligible cigarette smokers were randomly allocated to study groups; 714 men composed the intervention group, and 731 men were in the normal care group.

Men in the intervention group were recalled for a series of personal interviews with the physician. First, each received a letter inviting him to an appointment to discuss the results of his previous examination. At that visit the reason for recall was presented: evidence in his particular case that smoking represented more than the average risk to his future health, not the discovery of disease. The scientific evidence that stopping smoking was likely to bring benefits was explained and illustrated by charts, with the emphasis

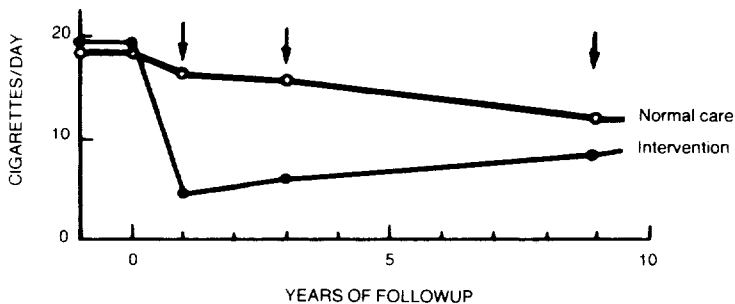


FIGURE 2.—Mean daily cigarette consumption by year of followup for the Whitehall intervention study

SOURCE: Rose et al. (57).

throughout on the evidence for the positive benefits and practicalities of stopping rather than on the hazards of continuing to smoke.

A full report of the screening examination results and information that further action was in his hands was sent to the practitioners of men in the normal care groups. The men were not made aware that they were involved in a trial. At the 1-year and 3-year points in the study, they were asked to return for an examination to help research. Examinations were popular because most men saw them as beneficial checkups. The questionnaire response rates among survivors were 84 percent at 1 year and 83 percent at 9 years. Dropouts were mainly retirees. The proportion of responders in the intervention group who were not smoking any cigarettes was 63 percent at 1 year, decreasing to 55 percent at 9 years; initially, all of those in the study were smokers. Figure 2 shows the trends in stated numbers of cigarettes smoked in the intervention group. After 1 year, consumption in the intervention group was one-quarter of the normal care group level. By 9 years, the estimate of cigarette consumption for intervention men was 70 percent of that for the normal care controls. Over the 10 years, the net apparent reduction in the intervention group averaged 7.6 cigarettes/day (–53 percent), compared with the control level, as shown in Figure 2 and Table 4.

During the 10 years of followup, there were 128 deaths in the control group compared with about 130 deaths expected from the age-specific rates for England and Wales in 1974, as shown in Table 9. The fact that all men entering the trial were high risk smokers should have increased the observed deaths, but this may have been offset by the “healthy worker” effect in an occupational study group or by the selection process that excluded very sick men. Deaths were also close to national levels for coronary heart disease (111 observed, 94 expected), lung cancer (42 observed, 35 expected), and other

TABLE 6.—Summary of deaths and intervention/control differences from coronary heart disease, all other causes, and all causes in four randomized controlled trials

Disease	Observed deaths in intervention group	Expected deaths based on control group	Percentage difference ¹ (O-E)/E
Coronary heart disease			
MRFIT	115	123.8	-7.1
Whitehall	49	60.6	-19.1
Oslo	6	13.3	-55.4
WHO	367	396.4	-7.4
Unweighted total	537	594.1	-9.6 (p=.02)
All other causes			
MRFIT	150	135.8	+10.5
Whitehall	74	64.4	+14.9
Oslo	10	9.7	+3.1
WHO	630	627.7	+0.4
Unweighted total	864	837.6	+3.2
All causes			
MRFIT	265	259.6	+2.1
Whitehall	123	125.0	-1.6
Oslo	16	23.0	-30.6
WHO	997	1024.1	-2.7
Unweighted total	1401	1431.7	-2.1

¹ Unless indicated with a p value, differences are not statistically significant ($p > 0.05$), based on a two-tailed test for a Poisson variable.

cancers (40 observed, 41 expected). Seventy-two percent of deaths occurred in a hospital, and in 45 percent there was an autopsy. Additional data were obtained from the National Cancer Register of cases histologically confirmed either by biopsy or at autopsy for deaths from other causes.

Table 5 shows that the 10-year CHD death rate was 8.5 percent (62 deaths) for the normal care group and 6.9 percent (49 deaths) for the intervention group, a proportionate change of -19 percent (95 percent confidence limit of -43 to +18 percent). Among the 369 men who entered the trial with evidence of myocardial ischemia (angina pectoris, history of possible myocardial infarction, or positive electrocardiogram) the reduction was -23 percent compared with -11 percent in those without such evidence. The number of deaths from cardiovascular causes other than CHD was 12 in the normal care group and 13 in the intervention group.

Mortality from all causes was initially higher (though not significantly so) in the intervention group, but during the last 6 years of the trial, the rates were higher in the normal care group. During the whole 10 years, 123 intervention men (17.2 percent) died, compared

with 128 (17.5 percent) of the normal care group—a proportionate change of -2 percent (95 percent confidence limits of -22 percent to +23 percent). Causes of death were also grouped according to whether or not they were smoking related. The smoking-related causes included coronary heart disease, chronic bronchitis, and cancers of the respiratory tract, esophagus, urinary tract, and pancreas. There were 92 such deaths in the normal care group and 81 in the intervention group, a proportionate change of -9 percent (95 percent confidence levels of -31 percent to +20 percent).

The trial was designed to test whether the total reduction in cardiorespiratory disease among middle-aged men was as large as that indicated by the observational studies of ex-smokers. Its size was planned in the expectation that incidence as well as mortality data would be available; when this proved unattainable, the resultant loss of power was partly offset by extending the mortality followup to 10 years.

At 1-year followup, almost two-thirds of the intervention subjects had given up cigarettes altogether, while others claimed to be smoking less than before. Unlike the MRFIT study, objective tests of smoking behavior were not made here. However, the authors felt that those who reported complete cessation were generally truthful, while those claiming to have cut down may have been exaggerating. The reports were based on questionnaires completed at home, with little external pressure; they were largely consistent over the ensuing years. The progressively narrowing gap between the two groups was due mainly to a gradual reduction in smoking by the normal care men. Although the size of the gap may have been overestimated, there is no doubt that throughout the earlier years of the trial it was large.

Over the trial as a whole, the intervention group's level of total smoking exposure was estimated as about half that of the normal care group, implying that the effects of complete cessation might be substantially more than those observed in the trial. The results for total mortality represented the approximate balance of a favorable trend for smoking-related diseases and an adverse trend for non-lung cancers. After an exhaustive analysis of the data, the Whitehall investigators think the difference in non-lung-cancer mortality in this trial was more likely due to chance than to an effect of intervention. Such evidence as there is for the latter view should be considered as a hypothesis for further study, not as the basis for conclusions or for any recommendation to smokers.

Oslo Study

The purpose of the Oslo study was to find out whether the cessation of smoking and the lowering of high levels of blood lipids by dietary changes, if maintained for many years, would lead to

reduction in the incidence of first attacks of CHD in men aged 40 to 49 (26, 27, 28). All Oslo men aged 40 to 49 were invited for screening of coronary risk factors during 1972-73, and 65 percent (16,202 men) attended. From this cohort, healthy normotensive men were selected for a controlled trial if they had serum cholesterol levels (mean of two measurements) of 290 to 380 mg/dl, coronary risk scores (based on cholesterol levels, smoking habits, and blood pressure) in the upper quartile of the distribution, and systolic blood pressures (mean of two measurements) below 150 mm Hg. Those selected had normal ECGs at rest and were free of any cardiovascular disease, chest pain on exercise, clinical diabetes mellitus, fasting blood sugar levels above 135 mg/dl, cancer, disabling disease, psychopathological disease, and alcoholism.

Men who met the selection criteria were sent a letter explaining the experimental design of the trial; 97 percent were found willing to participate. There were no significant differences between the intervention and control groups for subject factors such as age, history of CHD symptoms, cigarette consumption and smoking status, serum cholesterol and triglyceride, systolic blood pressure, and diet. After the screening examination, two reexaminations were made before randomization, the first of these when the subjects were fasting.

Each of the men in the intervention group was individually talked with for 10 to 15 minutes by the investigator and introduced to the risk factor concept and the purpose of the study. Anti-smoking advice was given individually to all smokers in the intervention group. They were informed that cessation of smoking might be of special importance for those with high blood lipid levels. In addition, the dietitian established a diet record for each man and gave extensive dietary advice based on this record. Other risk factors were not subjected to intervention. Followup exams were made every 6 months for intervention subjects and every 12 months for controls.

The intervention of advice on smoking and eating habits resulted in changes in risk variables. Tobacco consumption, expressed as the number of cigarettes smoked per man per day, fell about 45 percent more in the intervention group than in the controls, as seen in Table 4. Pipe smoking was included, taking one pack of pipe tobacco weekly to equal seven cigarettes daily. The percentage of cigarette smokers fell by only 16 percent more. The data were assessed by a questionnaire and by the thiocyanate method. The mean difference in serum cholesterol between the two groups during the 5 years was 13 percent.

As the design of the study was based on CHD evidence, events of myocardial infarction (MI) plus sudden death were most important. CHD mortality (fatal MI plus sudden coronary deaths) was 55 percent lower in the intervention group as compared with the

TABLE 7.—Comparison of coronary heart disease incidence rates (r) and cases (n) in two randomized controlled trials

	Intervention group		Control group		Percentage difference ¹
	r _i	n _i	r _c	n _c	
Oslo: 5-year results					
Fatal MI and sudden coronary deaths	.0099	6	.0222	14	-55.4
Nonfatal MI	.0215	13	.0350	22	-38.6
Total CHD incidence	.0314	19	.0573	36	-45.2 (p = .03)
WHO: 6-year results					
Fatal MI and sudden coronary deaths	.0150	367	.0162	355	-7.4
Nonfatal MI	.0195	406	.0203	401	-3.9
Total CHD incidence	.0318	773	.0331	756	-3.9

¹ Unless indicated with a p value, differences are not statistically significant ($p > 0.05$), based on a two-tailed test for a Poisson variable.

control group, but the difference was not statistically significant ($p > 0.05$), as shown in Tables 5 and 7. Total CHD incidence, which included fatal and nonfatal MI and sudden death, was 45 percent lower in the intervention group than in the control group, and this difference was significant ($p < 0.05$), as shown in Table 7. This is the only trial to date to show a significant reduction in CHD incidence. All cases of sudden death satisfied the diagnostic criteria for coronary death except one unexplained sudden death. The total coronary deaths, which included fatal MI and sudden death, were lower, but not significantly lower in the intervention group than in the control group.

An estimate was made of the proportion of the difference in total CHD incidence between the two groups (36 versus 19 cases) due to the reduction in cigarette consumption and of the proportion due to the reduction in serum cholesterol using logistical regression techniques (28). The percentage of the decline in incidence that was due to reduction in cigarette consumption was estimated to be 26 percent among smokers only, predicting a difference between groups of 3.9 cases, out of a total difference of 17 CHD cases. Similar procedures indicated that the percentage due to cholesterol changes was 60 percent for all men, predicting a difference in CHD incidence of 10.1 cases. It seems, therefore, that the change in cigarette consumption caused about 25 percent of the difference in CHD incidence between the two groups and that the difference was due mainly to the reduction in serum cholesterol. The difference between the groups was 17 cases: 14 can be explained by this analysis, and the other 3 cases may be due to unexplained intervention effects or to chance.

Community-Based Intervention Trials

WHO European Collaborative Trial

As set out in the recent WHO report on the prevention of coronary heart disease (70), effective prevention must involve the population as a whole: A high incidence in the population reflects a mass elevation of risk factors, and most cases of the disease occur in the large number of people with moderate elevations rather than in the high risk minority. The first issue of public health policy, therefore, is to know the effect of population-based prevention, using resources that could reasonably be afforded. Thus, a trial of CHD prevention has been undertaken by collaborators in Belgium, Italy, Poland, Spain, and the United Kingdom (68, 69). It involved the random allocation of 44 factory pairs, employing 63,732 men aged 40 to 59, either to a cardiovascular screening and health education intervention program or to a control group. Separate analyses have been prepared for Belgium factories (35, 36) and United Kingdom factories (52, 53), but these subgroups are not discussed in detail here.

Randomization of individuals in a trial of community health education is not feasible, so a somewhat unusual design was used that randomized entire communities, which in this trial were factories or other large industrial groups. They were arranged in matched pairs and randomized, one to intervention and the other to serve as a control. All men aged 40 to 59 in the intervention factories were invited to complete a questionnaire and take part in a simple cardiovascular screening examination during working hours; 87 percent responded. On the basis of a multifactorial scoring system for risk factor levels (age, job activity, cigarettes smoked per day, systolic blood pressure, and serum cholesterol), 15 percent or more of the men in each factory were designated as high risk. A general campaign of risk factor modification was undertaken with posters, brochures, personal letters, progress charts, and group discussions and included advice on reducing or stopping cigarette smoking, losing weight, lowering serum cholesterol, and increasing leisure physical activity. The high risk men received more individual attention, in addition to the general educational program, including a series of personal sessions with the factory or project physician. All men with mild hypertension were treated with diuretics or other drugs in the factory or were referred to a personal physician. Drugs were not employed to lower serum cholesterol. Annually, a random sample of men was rescreened. All high risk men were seen at every anniversary in some centers, or in other centers, at particular anniversaries. All men remaining in employment at the end of the 5- or 6-year intervention period were offered a final examination.

In the control factories, a 10 percent random sample of men was screened initially, and the same 10 percent were asked to return after 2 years, again at 4 years, and then at the final screening at 5 or

6 years, when all remaining men in the original cohort, aged 40 to 59 at the start, were offered screening. It was therefore possible to compare risk factor levels at the start between all screened intervention men and 10 percent of controls, between a 5 percent random sample or more of the intervention men and the same 10 percent of the controls at 2 years and 4 years, and between all remaining men in both sets of factories at the final screening. Numbers were reduced by death, by leaving employment, and by nonresponse to the invitation on the screening day. The risk factor score used in each intervention factory to designate high risk men was applied to the 10 percent of the screened men in the paired control factory in order to identify those who would act as high risk controls for purposes of measuring risk factor change. Incidence and mortality results are now available (69) from this controlled trial, involving randomization of 66 factories (49,781 men) in the United Kingdom, Belgium, Italy, and Poland (Cracow). Results for Poland (Warsaw) are not yet complete, and the results have been separately presented for the United Kingdom (53) and Belgium (35). Net average reductions in risk factors (all subjects) were 8.9 percent for daily cigarettes, 1.2 percent for serum cholesterol, 0.4 percent for weight, 2.0 percent for systolic blood pressure, and 11.1 percent for a combined CHD risk estimate. Greater reductions occurred in high risk subjects (19.4 percent for the combined CHD risk estimate).

Tables 5 and 7 show that the net overall changes in CHD rates were -7.4 percent (95 percent confidence interval from -29 to +15 percent) for deaths (722 deaths) and -3.9 percent (95 percent confidence interval from -10 to +2 percent) for fatal CHD plus nonfatal myocardial infarction (1,502 cases). Among men aged 40 to 49 the reduction for this end-point was 15 percent; at ages 50 to 59 there was a small net increase. Deaths from all causes after an early adverse trend showed a -2.7 percent change overall. There were large differences between centers, ranging from a 5 percent net increase in CHD for the United Kingdom to a decrease of 24 percent in Belgium. In Belgium the decrease both in CHD incidence and in all deaths was significant at the 5 percent level (35). The effect on CHD in the different centers correlated broadly with their changes in risk factors. The authors concluded that a reduction in major coronary risk factors in industrial populations is possible, but it depends on adequate resources. The results support the hypotheses that CHD risk in middle-aged men is reversible and that community intervention can be beneficial; however, additional followup is necessary to determine if there are statistically significant reductions in CHD and total mortality commensurate with the risk factor changes in the entire factory population.

North Karelia Study

The purpose of the North Karelia, Finland, project was to provide a systematic comprehensive community program to reduce the currently high mortality and morbidity from CHD, primarily by reducing the known cardiovascular risk factors of smoking, serum cholesterol, and blood pressure, while promoting early detection, treatment, and rehabilitation in people with severe CHD (48, 54, 56). The focus was on middle-aged males; women were included, but are not discussed here. A further test was made of the feasibility and the effect of this approach in the control of CHD and other health problems on a nationwide level.

Baseline data concerning cardiovascular diseases and their main risk factors in the target community of North Karelia and in the control area of Kuopio were studied in detail. To do this, a representative random 6.6 percent sample was drawn for the 1972 population of the two communities by using the national population register. The sample comprised men and women born during 1913 to 1947 (then aged 25 to 59). About 52 percent of the men in the study were current smokers, and each smoker consumed an average of 18 cigarettes per day. Their mean levels of serum cholesterol and blood pressure were above normal, as seen in Table 4.

Owing to the high general level of the known CHD risk factors in this population, a comprehensive program was integrated into the health and social services of the community. The program consisted of (1) information given to the public, especially about the practical activities directed toward the risk factors in the community, by means of media (newspapers, radio, leaflets, posters, and stickers) and at health information education meetings and public campaigns, schools, and places of work; (2) organization of services by systematically integrating the program into existing services and creating new services when necessary, such as special supporting services for stopping smoking; (3) training personnel for the special practical tasks of the program; (4) environmental services to support the desired lifestyle, for example, with regard to smoking restrictions; and (5) internal information services to support registers for hypertension, myocardial infarction, and stroke and to help with followup surveys.

No differences were found in the prevalence of smoking between the target area and the control area at the beginning of the study in 1972. By 1977, there was a nonsignificant net reduction of 2.5 percent in the prevalence of smoking among North Karelia men relative to the control men. But when the reported amount of smoking was taken into account, a net 9.8 percent reduction was significant. This was a result of the finding that in 1972 North Karelian men smoked more than did those in the control area. There was a highly significant 4.1 percent net reduction of mean serum

TABLE 8.—Death rates and relative risk of death in those MRFIT subjects who quit at 1 year and those who continued smoking (average further followup, 6 years)

Smoking status at entry	Smoking status at year 1		CHD death rates		Total death rates	
	No. quit	No. continued	Percent quit	Percent continued	Percent quit	Percent continued
By level of smoking						
1-29 cigs/day	613	1,827	1.47	2.30	3.43	4.27
≥ 30 cigs/day	752	4,471	0.80	1.92	3.06	4.47
By group status						
Special intervention	991	2,842	1.11	2.04	2.93	4.68
Usual care	374	3,456	1.07	2.03	4.01	4.20
Total	1,365	6,298	1.10	2.03	3.22	4.41
Relative risk of death (quit/continued)						
By level of smoking						
1-29 cigs/day			0.64		0.80	
≥ 30 cigs/day			0.42		0.68	
By group status						
Special intervention			0.54		0.63	
Usual care			0.53		0.95	
Total			0.54		0.73	

cholesterol concentrations in the North Karelia men. At the start of the study, the mean serum cholesterol concentrations were higher in people in North Karelia than in the control area. There was a highly significant net reduction in systolic blood pressure from baseline for the North Karelia men. The prevalence of raised values in 1972 was similar among men in the two areas, and the net reduction in the prevalence of raised values in North Karelia was substantial and highly significant.

The estimates of CHD risk showed that in 1972 the North Karelians had a higher mean risk score than did the population in the control area. During the followup period, this difference was reversed among the men and there was a highly significant net reduction in the estimated CHD risk in North Karelia of 17.4 percent among the men. However, there were no significant relative reductions in CHD or total mortality among the North Karelia men compared with the control men as of 1977. However, a more recent analysis of mortality trends in Finland suggests that a longer period of followup may yield some significant relative reductions (55). Because of the different methodology used, the mortality results

TABLE 9.—Observed deaths in MRFIT and Whitehall studies and expected deaths based on general population and Framingham death rates

Study	Coronary heart disease			All causes		
	Observed in UC group	Expected (U.S. males) (1979)	SMR	Observed in UC group	Expected (U.S. males) (1979)	SMR
MRFIT study						
UC group (n=6438)						
Year						
1	9	~19	47	17	~48	35
2	20	~20	100	31	~50	62
3-6	75	~87	86	171	~223	77
7	20	~24	83	41	~63	65
1-7	124	~150	83	260	~384	68
		(Framingham)			(Framingham)	
1-7	124	~220	56	260	~515	50
UC smokers (n=4091)						
		(U.S. males) (1979)			(U.S. males) (1979)	
Years 1-7	89	~95	94	190	~244	78
Whitehall study						
NC group (n=731)						
		(English males) (1974)			(English males) (1974)	
Years 1-10	62	~48	129	128	~130	98

from this study have not been summarized in Tables 5 and 6, but the risk factor changes are shown in Table 4.

Comparison of Results From Intervention Trials and Epidemiologic Studies

Table 10 summarizes the expected reduction in CHD and total mortality for former smokers who stopped for 1 to 4 years or for 5 to 9 years, based on the three major observational studies in Table 1 (10, 11, 20, 49). This shows that, relative to current smokers, former smokers who have stopped for 1 to 9 years have a CHD mortality rate that is 25 percent less and a total mortality rate that is 18 percent less, in approximate terms. The cigarette smokers in the MRFIT and Whitehall studies have been subjected to smoking cessation intervention as the sole, or as a major, risk factor change. As seen in Table 4, smoking reduction in the intervention group relative to the control group was 31 percent in MRFIT and 54 percent in the Whitehall study, for an average reduction of about 40 percent in proportion of current smokers. This means that the expected reduction in mortality should be about 40 percent of that associated with total cessation; in other words, 10 percent for CHD mortality and 7 percent for total mortality. Combining the observed

TABLE 10.—Comparison of reductions in CHD and total mortality from observational studies of former smokers and from MRFIT and Whitehall intervention studies

	Coronary heart disease				Total mortality			
	British physicians	ACS 25-State	U.S. veterans	Average	British physicians	ACS 25-State	U.S. veterans	Average
Current smokers	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Former smokers, 1-4 yrs	.744	.613	.854	.737	.701	.934	.867	.834
Former smokers, 5-9 yrs	.887	.544	.873	.768	.861	.773	.809	.814
Average former smokers, 1-9 yrs				.753				.824
Percentage reduction, former smokers, 1-9 yrs				-24.7%				-17.6%
Percentage reduction, ~40% former smokers				-9.9%				-7.0%
	O_1	E_c		$\%diff(O-E)/E$	O_1	E_c		$\%diff(O-E)/E$
MRFIT smokers at S_1 (Table 7)	86	89.4		-3.7%	201	190.4		+5.6%
Whitehall smokers (Table 5)	49	60.6		-19.1%	123	125.0		-1.6%
Unweighted total	135	150.0		-10.0%	324	315.4		+2.7%
95% confidence interval				-24% → +7%				-8% → +15%

deaths from these two intervention groups shows a change in CHD mortality of -10 percent (95 percent CI from -26 percent to +6 percent) and a change in total mortality of +2.7 percent (95 percent CI from -9 percent to +14 percent). Thus, these two trials have yielded a result after 5 to 10 years of followup that is in good agreement with the observational studies for CHD deaths, but is not particularly close for total mortality. Because of the fairly large 95 percent confidence interval, the intervention results are consistent both with the observational studies and with no change at all. It must be noted that in MRFIT, other risk factor interventions took place on blood pressure and cholesterol, and interpretation of the results has raised the real possibility that an adverse effect on survival was associated with anti-hypertensive efforts in a specific subgroup of hypertensive patients, a finding which, if true, might mask a larger beneficial effect of smoking cessation.

As previously noted and as shown in Table 8, an analysis of survival in MRFIT participants who had been smokers at entry, demonstrates that those who quit at year 1 of followup had a 46 percent lower CHD mortality and a 27 percent lower all-cause mortality than those smokers who did not quit at year 1. This is further powerful evidence consistent with substantial improvement of survival associated with the cessation of cigarette smoking.

Conclusions

1. In the four intervention trials involving mortality followup of individual men for 5 to 10 years, the intervention groups had a combined total of 10 percent fewer CHD deaths than did the comparable control groups. Differences for other causes of death or for total deaths were not significant.
2. In these trials, the amount of cigarette smoking has been reduced 10 to 50 percent more in the intervention group than in the control group, demonstrating that intervention can alter smoking behavior.
3. In the two trials involving morbidity followup, the intervention groups had 4 and 45 percent lower total CHD incidence than did the respective control groups.
4. The relative reductions in CHD mortality in each of the four intervention studies involving individual followup are reasonably consistent with the reduction in CHD risk factors, and for a combination of all four studies, the reduction is statistically significant.
5. Numerous studies have shown that those who quit cigarette smoking experience a substantial decrease in CHD mortality and an improvement in life expectancy.

6. A number of prospective epidemiological studies indicate that former cigarette smokers substantially reduce their CHD and total death rates from that of current smokers.

References

- (1) AUSTRALIAN NATIONAL BLOOD PRESSURE STUDY. The Australian therapeutic trial in mild hypertension. Report of the Management Committee. *Lancet* 1(8181): 1261-1267, June 14, 1980.
- (2) BORHANI, N.O. Primary prevention of coronary heart disease: A critique. *American Journal of Cardiology* 40(2): 251-259, August 1977.
- (3) BOSSE, R., GARVEY, A.J., COSTA, P.T., Jr. Predictors of weight change following smoking cessation. *International Journal of the Addictions* 15(7): 969-991, October 1980.
- (4) CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity*. A ten year follow-up in a probability sample of 55,000 Swedish subjects age 18 to 69. Parts I and II. Stockholm, Karolinska Institute, 1975, 91 pp.
- (5) COOPERATIVE RANDOMIZED CONTROL TRIAL. Control of moderately raised blood pressure. Report of a cooperative randomized controlled trial. *British Medical Journal* 3(5877): 434-436, August 25, 1973.
- (6) CORONARY DRUG PROJECT RESEARCH GROUP. The Coronary Drug Project. Design, methods, and baseline results. *Circulation* 47(3, Supplement No. D): I-1-I-50, March 1973.
- (7) CORONARY DRUG PROJECT RESEARCH GROUP. Clofibrate and niacin in coronary heart disease. *Journal of the American Medical Association* 231: 360-381, January 27, 1975.
- (8) CORONARY DRUG PROJECT RESEARCH GROUP. Implications of findings in the Coronary Drug Project for secondary prevention trials in coronary heart disease. *Circulation* 63(6): 1342-1350, June 1981.
- (9) DAYTON, S., PEARCE, M.L., HASHIMOTO, S., DIXON, W.J., TOMIYASU, U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 40(1, Supplement No. II): II-1-II-63, July 1969.
- (10) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5395): 1399-1410, May 30, 1964.
- (11) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5396): 1460-1467, June 6, 1964.
- (12) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525-1536, December 25, 1976.
- (13) EDERER, F., LEREN, P., TURPEINEN, O., FRANTZ, I.D., Jr. Cancer among men on cholesterol-lowering diets. Experience from five clinical trials. *Lancet* 2(7717): 203-206, July 24, 1971.
- (14) ENSTROM, J.E. Trends in mortality among California physicians after giving up smoking: 1950-79. *British Medical Journal* 286: 1101-1105, April 2, 1983.
- (15) FARQUHAR, J.W. The community-based model of life style intervention trials. *American Journal of Epidemiology* 108(2): 103-111, August 1978.
- (16) FARQUHAR, J.W., WOOD, P.D., BREITROSE, H., HASKELL, W.L., MEYER, A.J., MACCOBY, N., ALEXANDER, J.K., BROWN, B.W., Jr., McALISTER, A.L., NASH, J.D., STERN, M.P. Community education for cardiovascular health. *Lancet* 1(8023): 1192-1195, June 4, 1977.
- (17) FRIEDMAN, G.D., PETITTI, D.B., BAWOL, R.D., SIEGELAUB, A.B. Mortality in cigarette smokers and quitters. Effect of base-line differences. *New England Journal of Medicine* 304(23): 1407-1410, June 4, 1981.
- (18) GORDON, T., KANNEL, W.B., MCGEE, D., DAWBER, T.R. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham study. *Lancet* 2(7893): 1345-1348, December 7, 1974.

- (19) HAMILTON, M., THOMPSON, E.N., WISNIEWSKI, T.K.M. The role of blood-pressure control in preventing complications of hypertension. *Lancet* 1(7327): 235-238, February 1, 1964.
- (20) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 127-204.
- (21) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167-182, August 1969.
- (22) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159-1172, March 8, 1958.
- (23) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294-1308, March 15, 1958.
- (24) HELGELAND, A. Treatment of mild hypertension: A five year controlled drug trial. The Oslo study. *American Journal of Medicine* 69(5): 725-732, November 1980.
- (25) HIRAYAMA, T., HAMANO, Y. Smoking and the relationship with rates for major causes of death—An epidemiological study based upon 13 years of continued observation of 265,118 adults over 40 at 29 selected health centers throughout Japan. *Eisei no Shibyō* 28(4): 1-18, April 1981.
- (26) HJERMANN, I. Smoking and diet intervention in healthy coronary high risk men. Methods and 5-year followup of risk factors in a randomized trial. The Oslo study. *Journal of the Oslo City Hospitals* 30(1): 3-17, January 1980.
- (27) HJERMANN, I., VELVE BYRE, K., HOLME, I., LEREN, P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo study group of a randomised trial in healthy men. *Lancet* 2(8259): 1303-1310, December 12, 1981.
- (28) HOLME, I. On the separation of the intervention effects of diet and antismoking advice on the incidence of major coronary events in coronary high risk men. The Oslo study. *Journal of the Oslo City Hospitals* 32(3/4): 31-54, March/April 1982.
- (29) HUGHES, G.H., HYMOWITZ, N., OCKENE, J.K., SIMON, N., VOGT, T.M. The Multiple Risk Factor Intervention Trial (MRFIT). V. Intervention on smoking. *Preventive Medicine* 10(4): 476-500, July 1981.
- (30) HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *Journal of the American Medical Association* 242(23): 2562-2571, December 7, 1979.
- (31) HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP. Five-year findings of the Hypertension Detection and Follow-up Program. II. Mortality by race, sex and age. *Journal of the American Medical Association* 242(23): 2572-2577, December 7, 1979.
- (32) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 and one-half years of observation. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1-125.

- (33) KLEBBA, A.J., DOLMAN, A.B. Comparability of mortality statistics for the seventh and eighth revisions of the International Classification of Diseases, United States. *Vital and Health Statistics. Series 2, Number 66.* U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, DHEW Publication No. (HRA)76-1340, October 1975, 93 pp.
- (34) KLEBBA, A.J., SCOTT, J.H. Estimates of selected comparability ratios based on dual coding of 1976 death certificates by the eighth and ninth revisions of the International Classification of Diseases. *Monthly Vital Statistics Report.* Vol. 28, No. 11, Supplement. U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, DHEW Publication No. (PHS)80-1120, February 29, 1980, 19 pp.
- (35) KORNTITZER, M., DeBACKER, G., DRAMAIX, M., KITTEL, F., THILLY, C., GRAFFAR, M., VUYLSTEEK, K. Belgium Heart Disease Prevention Project: Incidence and mortality results. *Lancet* 1(8333): 1066-1070, May 14, 1983.
- (36) KORNTITZER, M., DeBACKER, G., DRAMAIX, M., THILLY, C. The Belgian Heart Disease Prevention Project. Modification of the coronary risk profile in an industrial population. *Circulation* 61(1): 18-25, January 1980.
- (37) KULLER, L., MEILAHN, E., TOWNSEND, M., WEINBERG, G. Control of cigarette smoking from a medical perspective. *Annual Review of Public Health* 3: 153-178, 1982.
- (38) LEREN, P. The Oslo diet-heart study: Eleven-year report. *Circulation* 42(5): 935-942, November 1970.
- (39) MANN, J.I., MARR, J.W. Coronary heart disease prevention: Trials of diets to control hyperlipidaemia. In: Miller, N.E., Lewis, B., (Editors). *Lipoproteins, Atherosclerosis and Coronary Heart Disease.* Volume 1. Amsterdam, Elsevier, 1981, pp. 197-210.
- (40) MEDICAL RESEARCH COUNCIL RESEARCH COMMITTEE. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 2(7570): 693-700, September 28, 1968.
- (41) METROPOLITAN LIFE INSURANCE COMPANY. Effects of selection on mortality. *Statistical Bulletin* 52: 9-11, June 1971.
- (42) MIETTINEN, M., TURPEINEN, O., KARVONEN, M.J., ELOSUO, R., PAAVILAINEN, E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes. *Lancet* 2(7782): 835-843, October 21, 1972.
- (43) MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *Journal of the American Medical Association* 248(12): 1465-1477, September 24, 1982.
- (44) NATIONAL CENTER FOR HEALTH STATISTICS. *Health, United States, 1982.* U.S. Department of Health and Human Services, Public Health Service, Health Resources Administration, National Center for Health Statistics, DHHS Publication No. (PHS)83-1232, December 1982, 191 pp.
- (45) NATIONAL DIET-HEART STUDY RESEARCH GROUP. The national diet-heart study final report. *Circulation* 37(3, Supplement No. 1): I-1-I-428, March 1968.
- (46) NAUKKARINEN, V. *The Feasibility of Administering Preventive Treatment for Coronary Heart Disease to Middle-Aged Men.* Helsinki, Finland, K.J. Gummerus Osakeyhtiön Kirjapainossa Jyvaeskylaessae, 1981.
- (47) NOPPA, H., BENGTTSSON, C. Obesity in relation to smoking: A population study of women in Göteborg, Sweden. *Preventive Medicine* 9(4): 534-543, July 1980.

- (48) PUSKA, P., TUOMILEHTO, J., SALONEN, J., NEITTAANMAKI, L., MAKI, J., VIRTAMO, J., NISSINEN, A., KOSKELA, K., TAKALO, T. Changes in coronary risk factors during comprehensive five-year community programme to control cardiovascular diseases (North Karelia project). *British Medical Journal* 2(6199): 1173-1178, November 10, 1979.
- (49) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213-222, May-June 1980.
- (50) ROSE, G., HAMILTON, P.J.S. A randomised controlled trial of the effect on middle-aged men of advice to stop smoking. *Journal of Epidemiology and Community Health* 32(4): 275-281, December 1978.
- (51) ROSE, G., HAMILTON, P.J.S., COLWELL, L., SHIPLEY, M.J. A randomised controlled trial of anti-smoking advice: 10-year results. *Journal of Epidemiology and Community Health* 36(2): 102-108, June 1982.
- (52) ROSE, G., HELLER, R.F., PEDOE, H.T., CHRISTIE, D.G.S. Heart disease prevention project: A randomised controlled trial in industry. *British Medical Journal* 1(6216): 747-751, March 15, 1980.
- (53) ROSE, G., TUNSTALL-PEDOE, H.D., HELLER, R.F. UK Heart Disease Prevention Project: Incidence and mortality results. *Lancet* 1(8333): 1062-1066, May 14, 1983.
- (54) SALONEN, J.T., PUSKA, P., KOTTKE, T.E., TUOMILEHTO, J. Changes in smoking, serum cholesterol and blood pressure levels during a community-based cardiovascular disease prevention program—The North Karelia project. *American Journal of Epidemiology* 114(1): 81-94, July 1981.
- (55) SALONEN, J.T., PUSKA, P., KOTTKE, T.E., TUOMILEHTO, J., NISSINEN, A. Decline in mortality from coronary heart disease in Finland from 1969 to 1979. *British Medical Journal* 286(6381): 1857-1860, June 11, 1983.
- (56) SALONEN, J.T., PUSKA, P., MUSTANIEMI, H. Changes in morbidity and mortality during comprehensive community programme to control cardiovascular diseases during 1972-7 in North Karelia. *British Medical Journal* 2(6199): 1178-1183, November 10, 1979.
- (57) SELTZER, C.C. Smoking and coronary heart disease: What are we to believe? *American Heart Journal* 100(3): 275-280, September 1980.
- (58) SHAPIRO, S., WEINBLATT, E., FRANK, C.W., SAGER, R.V. Incidence of coronary heart disease in a population insured for medical care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. *American Journal of Public Health* 59(Supplement 6): 1-101, June 1969.
- (59) TURPEINEN, O., KARVONEN, M.J., PEKKARINEN, M., MIETTINEN, M., ELOSUO, R., PAAVILAINEN, E. Dietary prevention of coronary heart disease—The Finnish mental hospital study. *International Journal of Epidemiology* 8: 99-118, 1979.
- (60) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79-50066, 1979, 1136 pp.
- (61) U.S. PUBLIC HEALTH SERVICE. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.
- (62) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM)71-7513, 1971, 458 pp.