

## Chapter 2. Brief description of the Multiple Risk Factor Intervention Trial<sup>1,2</sup>

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**ABSTRACT** The Multiple Risk Factor Intervention Trial (MRFIT) was one of the coronary heart disease prevention trials recommended to the National Heart and Lung Institute in 1971 as an alternative to a national single-factor dietary trial, which was judged to be infeasible. MRFIT was a randomized, primary prevention trial, conducted at 22 US clinical centers from 1973 to 1982 to test whether lowering elevated serum cholesterol and diastolic blood pressure and ceasing cigarette smoking would reduce coronary heart disease mortality. Men 35–57 y of age ( $n = 12\,866$ ) with one or more of these risk factors were randomly assigned to the special intervention (SI) or usual care (UC) group and followed for 6–8 y. UC men were given information on risk factors, referred to their usual sources of care, and reexamined annually. SI participants received group and individual counseling on a fat-modified diet, a stepped-care drug treatment program for diastolic hypertension (after an initial attempt at blood pressure control by weight reduction, if indicated), and, for cigarette smokers, counseling aimed at cessation. SI men had risk factor assessments every 4 mo and annual examinations that were generally identical to those given to UC men and that always included measurement of blood cholesterol concentration. A listing of variables measured at each visit along with the design and major mortality results of MRFIT are included in this chapter. *Am J Clin Nutr* 1997;65(suppl):191S–5S.

**KEY WORDS** Nutrition, clinical trial, MRFIT description

### INTRODUCTION

The Multiple Risk Factor Intervention Trial (MRFIT) was a large, multicenter, randomized clinical trial designed to test whether middle-aged men with one or more of three major risk factors for coronary heart disease (CHD)—cigarette smoking, high blood pressure, and elevated serum cholesterol—would experience a lower CHD death rate as the result of participation in a multifactor intervention program for modifying these risk factors.

Men found to be eligible at the completion of the screening phase were randomly assigned to one of two groups: the special intervention (SI) group ( $n = 6428$ ), who participated in the specially designed intervention program, or the usual care (UC) group ( $n = 6438$ ), who were referred back to their usual source of health care. All men were seen at least annually for risk factor, morbidity, and other assessments. Men in the SI group were seen more often: 4 and 8 mo after each annual visit for limited risk factor assessment, approximately weekly during

the first year's 10-session intensive intervention program, frequently for clinic visits during the early phase of therapy for those who became hypertensive, and during special clinic visits for those participating in ad hoc intervention programs designed during the course of the trial to improve risk factor modification in selected groups.

Each participant had a follow-up period of  $\geq 6$  y. With entry (randomization) into the trial spread over a 2-y period and the termination of active intervention on the sixth anniversary of date of entry for the last man randomly assigned, the intervention and follow-up periods ranged from 6 to 8 y, with an average duration of 6.9 y. Results of the trial at the termination of active intervention were reported previously (1–5). Mortality follow-up has continued beyond the end of active intervention; reports based on 10.5 and 16 y of follow-up have also been published (6–8).

### BACKGROUND

Early evidence for increased risk of death from CHD in persons with elevated blood cholesterol concentrations and high blood pressure and who smoke cigarettes was derived, in large part, from pioneering cardiovascular cohort studies conducted in the 1950s and 1960s. Data from several of these studies, including the Albany Civil Servant Study (NY), the Framingham Heart Study (MA), the Peoples Gas Company Study (Chicago), the Tecumseh Community Study (MI), and the Western Electric Study (Chicago) were pooled, analyzed, and eventually published as a special report documenting these variables as risk factors for death from CHD (9). These studies formed the conceptual basis for the design of MRFIT. Although obviously not available for the planning of MRFIT, the data gathered from the  $> 360\,000$  men who attended the first screening visit for the MRFIT have since provided independent documentation of the risk factor relations indicated from these earlier studies. Additionally, because of the unusually large size of the screening cohort, these data yielded with unprece-

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mented precision quantitative estimates of the risks associated with various levels of these factors (10). The data in **Table 1**, which are based on an average follow-up of these men of 16 y, indicate the strong bivariate gradient of CHD mortality risk for diastolic blood pressure and serum cholesterol for nonsmokers and for cigarette smokers; CHD mortality risks were much higher for cigarette smokers than for nonsmokers. Gradients for systolic blood pressure (not shown) were even stronger than for diastolic (10).

MRFIT was a direct result of recommendations made in 1971 by a Task Force on Arteriosclerosis appointed by the Director of the National Heart and Lung Institute (11). This report included several major thrusts. First, having reviewed the experience of the National Diet-Heart Feasibility Study, most of the Task Force did not favor the initiation of a national diet-heart trial in the general population of the United States. This conclusion was based primarily on perceived logistical difficulties and estimated high costs associated with a long-term trial large enough to meet the proposed sample size requirements. A 7–10-y trial of 24 000–115 000 persons was estimated to range in cost from \$500 million to more than \$1 billion. Second, the Task Force was concerned that those individuals adhering to a diet regimen would modify other risk factors, making interpretation of the results difficult. This concern led the group to recommend that the Institute “undertake multiple risk factor intervention trials in individuals at high risk because of combinations of elevated serum lipids, hypertension, and cigarette smoking” (11). The view of the Task Force that “these trials will have the merit of demonstrating whether or not intervention can prevent the complications of human arteriosclerosis since this is the crucial question as yet unanswered by direct experiment” implies that they considered the determination of whether CHD could be prevented to have priority over determining whether dietary modification alone would reduce CHD morbidity and mortality (11). This is underscored by their acknowledgment that “these [multiple risk factor] trials would not delineate the effects of the various individual risk factors.”

### SAMPLE SIZE AND POWER CONSIDERATIONS

The sample size goal of 12 000 men was derived from 1) an estimate of the expected 6-y CHD death rate for UC men,

2) a projection of the effect the proposed intervention might have in lowering such a rate for the SI men, and 3) a requirement for a reasonably high probability of detecting such an effect if it existed (12). The 6-y CHD death rate for UC men was projected to be 29.0 deaths per 1000 men. The reduction in risk that would be expected based on the anticipated intervention effects led to an estimate of 21.3 deaths per 1000 for SI men. With the total of 12 866 men, there would be a probability of 0.88 of detecting the expected difference (29.0 versus 21.3) with a one-sided test of difference between proportions at the 0.05 level of significance. The anticipated intervention effects for purposes of sample size estimation were 1) a 10% reduction of serum cholesterol if  $\geq 220$  mg/dL, otherwise no change; 2) a 10% reduction of diastolic blood pressure if  $\geq 95$  mm Hg, otherwise no change; and 3) graded reductions for smokers as follows: 25% average reduction in cigarettes smoked per day for smokers of  $\geq 40$  cigarettes/d, 40% reduction for smokers of 20–39/d, and 55% for smokers of  $< 20$ /d. It was also assumed that the corresponding groups of UC smokers at entry would have reductions during the trial of 5%, 10%, and 15%, respectively, and that there would be no change in serum cholesterol or blood pressure in the UC group. Additional allowances were made for noncompliance by SI men.

Several numerical design assumptions made for purposes of sample size calculation became, in retrospect, questionable. First, the expected 6-y death rate for UC men was a considerable overestimate. Self-selection of health-conscious men into the trial, screening criteria that excluded certain high-risk men, nonnegligible risk factor improvement in UC men during the trial, and the use of Framingham data from an earlier decade for estimation are likely factors contributing to this overestimation. Second, the expected reduction in 6-y risk for SI compared with UC men, based on the anticipated intervention effects for SI men, may also have been overestimated as a result of factors such as nonnegligible changes among the UC group, the possibility of an unfavorable response to part of the antihypertensive treatment protocol, the possibility of a longer than anticipated lag period for intervention effects to become evident, and the possibility of differential intervention effects among subgroups of the trial cohort.

**TABLE 1**

Age-adjusted coronary heart disease death rates per 10 000 person-years by concentration of serum cholesterol and diastolic blood pressure (DBP)

DBP quintile (mm Hg)	Cholesterol quintile (mg/dL) <sup>1</sup>				
	< 182	182–202	203–220	221–244	$\geq 245$
Nonsmokers (n = 202 504)					
< 76	4.8	6.8	7.1	8.9	13.4
76–80	5.6	7.8	8.9	11.4	18.7
81–85	6.3	10.1	11.6	12.7	19.1
86–91	9.3	11.6	11.8	17.2	26.5
$\geq 92$	13.1	17.0	19.4	25.6	35.2
Cigarette smokers (n = 113 595)					
< 76	12.2	16.2	17.7	26.3	33.2
76–80	16.3	19.1	22.8	29.0	39.3
81–85	15.7	21.1	25.4	31.0	42.3
86–91	21.8	26.8	37.4	41.1	52.9
$\geq 92$	31.2	41.9	49.9	57.4	65.8

<sup>1</sup> To convert to SI units (mmol/L), multiply by 0.02586.

## SCREENING AND RANDOMIZATION

The screening phase of MRFIT was conducted from 1973 to 1975; the last member of the cohort was randomly assigned on February 28, 1976 (13). The primary purpose of the first of the three screening visits was to ascertain risk factor eligibility for the 361 662 men seen at this visit at 22 clinical centers in 18 US cities. On the first screening visit, blood pressure was measured three times, the number of cigarettes smoked per day was ascertained, and a blood sample was drawn for serum cholesterol measurement. In addition to collection of data on age and ethnic group, several questions about disease history and geographic mobility were asked for early exclusion purposes. Men with a serum cholesterol concentration  $\geq 350$  mg/dL or diastolic blood pressure  $\geq 115$  mm Hg were excluded and referred to a source of medical care. Serum cholesterol was determined at one of 13 local laboratories that were standardized by the Lipid Standardization Laboratory of the Centers for Disease Control and Prevention. To establish risk factor eligibility, a risk function that combined the three risk factor measurements, with coefficients based on data from the Framingham Heart Study, served as the criterion. With use of this function, men who were eligible did not necessarily have all three risk factors; for example, only 64% of the randomly assigned cohort smoked cigarettes.

Of the > 25 000 men found to be risk factor eligible at the first visit, 22 080 attended the second screening visit, which included the following procedures: blood pressure measurement, height and weight measurement, a urine test for sugar and protein, recording of a 12-lead resting electrocardiogram, collection of a fasting plasma sample (sent to a central laboratory for determination of plasma total cholesterol, triglycerides, high-, low-, and very-low-density-lipoprotein cholesterol), collection of a fasting serum sample (sent to the central laboratory for determination of uric acid, creatinine, potassium, aspartate aminotransferase, glucose, and thiocyanate; hematocrit and white blood cell count were determined locally), glucose load followed by collection of a 1-h blood sample (also sent to the central laboratory for blood sugar determination), visual assessment of chylomicronemia, pulmonary function measurements, chest X-ray, and a physical examination. Several exclusion criteria not addressed at the first visit were applied based on the data collected at this visit. For example, a participant who refused to consider making changes in diet or smoking was excluded. Men consuming special diets were not excluded, however, unless the nutritionist judged the diet to be incompatible with the MRFIT eating pattern. Other specific exclusions relating to the likelihood of success in a nutrition intervention program are discussed in Chapter 3 (14).

Participants found eligible for the third screening visit were sent questionnaires on demographic, social, and behavioral factors; life events; and physical activity. Completed forms were reviewed with each of the 14 111 men who attended the third screening visit. Blood pressure was measured again, a resting electrocardiogram was recorded, and a treadmill exercise test was done with electrocardiographic recordings taken both during and after exercise. A 24-h dietary recall was recorded by a nutritionist who had been certified after a central standardized training program. Those who remained eligible for the trial at the conclusion of the third screening visit were invited to participate in the 6-y proposed program. A total of

12 866 men agreed to participate, gave their informed consent, and were randomly assigned, 6428 to the SI group and 6438 to the UC group. Each SI participant was asked to attend the initial intensive intervention program, a series of  $\approx 10$  weekly group sessions, and to bring his spouse (or homemaker) if possible. Men with elevated blood pressure were scheduled for a separate visit to determine whether or not drug or diet therapy would be initiated. The protocol allowed a 16-wk period of weight reduction and reduced salt intake before initiation of drug therapy for obese hypertensive participants.

## FOLLOW-UP VISITS

All men were asked to return once a year for measurement of risk factors, ascertainment of morbidity in the past year, and reassessment of selected variables measured at baseline. Specifically, the following were included each year (except as noted): medical and behavioral questionnaire; blood pressure measurement; weight measurement; resting electrocardiogram; fasting serum sample for determination of total cholesterol, triglycerides, uric acid, creatinine, potassium, aspartate aminotransferase, glucose, and thiocyanate; plasma sample for determination of total plasma cholesterol (at each annual visit except the first) and for high-, low-, and very-low-density-lipoprotein cholesterol (in alternate years); a 24-h dietary recall (except at the fourth annual visit for the SI group and at the fourth and fifth annual visits for the UC group); hematocrit, white blood cell count, and visual assessment of chylomicronemia; pulmonary function test; leisure time activity questionnaire (at the first, fourth, and sixth annual visits); physical examination; detailed smoking history; expired air carbon monoxide measurement (at the third and sixth annual visits); and a urine test for sugar and protein.

UC men were invited to only annual visits. In addition to attending intervention visits, SI men were requested to attend clinic visits 4 and 8 mo after being randomly assigned and after each annual visit for the purposes of measuring blood pressure, ascertaining number of cigarettes smoked/d, obtaining a record of food eaten during the 3 d before the visit, and obtaining a blood sample for serum cholesterol determination. For those taking antihypertensive medication, a more detailed blood chemistry profile was obtained.

## INTERVENTION

The MRFIT intervention program for SI men has been described in detail (15–18). The initial phase of intervention was an intensive integrated effort with a series of 10 weekly group sessions; this phase was followed by individual counseling by clinic staff. Although the intervention was designed to be an integrated one, there were specific objectives and means for achieving behavioral change and risk factor reduction for each of the three risk factor modalities. The nutrition intervention was structured to modify the participant's eating habits to obtain a reduction in percentage of energy from total fat and saturated fats, an increase in percentage of energy from polyunsaturated fats, a decrease in dietary cholesterol intake, and modification in intake of carbohydrate and alcohol. The general goal was to lower serum cholesterol concentrations in all SI men and the specific goal was to achieve a sustained



reduction of  $\geq 10\%$  for most of the men who had baseline concentrations  $\geq 220$  mg/dL. The program sought to encourage the development of lifelong shopping, cooking, and eating patterns rather than to impose a structured diet. Initially, eating patterns were recommended that would limit saturated fat intake to  $< 10\%$  of energy and dietary cholesterol to  $< 300$  mg/d; the contribution of polyunsaturated fats to energy was to be  $\geq 10\%$ . In 1976, or after  $\approx 1$  y of intervention on average, the nutrition pattern was modified to specify that saturated fat be  $< 8\%$  of energy and dietary cholesterol  $< 250$  mg/d. Weight reduction was sought for men whose weight was  $\geq 115\%$  of desirable weight by recommending reductions in energy intake and increases in moderate forms of physical activity. Methods and materials used in the nutrition intervention are discussed further in Chapter 3 (14).

The goal of the smoking intervention was cessation by those SI participants who smoked cigarettes. Conventional behavioral modification techniques were used throughout the trial; aversive techniques (eg, overdosing) and hypnosis were used for a few participants during the later years. The hypertension intervention required a determination of whether a man was hypertensive at baseline or became so during the trial. If a man was taking antihypertensive treatment prescribed by his personal physician (regardless of blood pressure) or if an untreated man had diastolic blood pressure  $\geq 90$  mm Hg on two consecutive monthly visits during the trial, he was considered to be hypertensive. Before drug prescription, weight reduction for overweight men and moderate reduction of sodium intake was attempted. Drugs were prescribed according to a stepped-care protocol beginning with either hydrochlorothiazide or chlorthalidone. Reserpine, hydralazine, guanethidine, or specified alternate drugs were added if appropriate blood pressure lowering was not achieved within specified time intervals. Changes in the drug regimen over the course of the trial included switching most diuretic-treated participants to chlorthalidone at a 50-mg maximum dose and the addition of propranolol as a second-step option.

### RISK FACTOR CHANGES

The intervention was successful in bringing about risk factor change. After 6 y of intervention, substantial reductions in the three major risk factors were observed in the SI group. Although reductions were also seen in the UC group, significantly greater reductions were observed in SI men (1). In general, most risk factor changes were accomplished early in the trial and were successfully maintained with gradual improvement during the intervention period. Diastolic blood pressure for SI men was lowered an average of 10.5 mm Hg, from 91.0 mm Hg at baseline (the average of pressures at the second and third screening visits) to 80.5 mm Hg 6 y later. For UC men the corresponding reduction was 7.3 mm Hg. At the time of randomization, 59% of the men in each group reported themselves as cigarette smokers. Six years later, the reported prevalence of cigarette smoking was 32% for SI men and 46% for UC men. Mean plasma cholesterol at baseline (determined at the second screening visit and therefore less affected by regression to the mean than the serum cholesterol measurement at the first visit that was used for eligibility determination) averaged 240 mg/dL. By year 6, plasma cholesterol was 12.1 mg/dL lower for SI

men and 7.5 mg/dL lower for UC men. These changes in plasma cholesterol were primarily due to reductions in low-density-lipoprotein cholesterol. The nonnegligible risk factor modification seen in UC men may have been due to several factors. Men in both the SI and UC groups were selected in part because they indicated a willingness to participate in a risk factor modification program should they be randomly assigned to the intervention group; ie, they were selected as an intervention-receptive group. This selection procedure together with widespread health education efforts to modify risk factors in the general population of the United States during the 1970s may have contributed to the observed risk factor changes in UC men.

### TRIAL RESULTS

At the end of active intervention on February 28, 1982, the mortality from CHD for SI men was 115/6428 (17.9 CHD deaths per 1000 men) and for UC men was 124/6438 (19.3 CHD deaths per 1000 men). This 7.1% lower rate for SI men than for UC men was not significant ( $P > 0.10$ ). Mortality from all causes for SI men was 265/6428 (41.2 deaths per 1000 men), 2% higher (also not significant) than the corresponding rate for UC men of 260/6438 (40.4 deaths per 1000 men).

With 1) the less than expected differential risk factor reduction mentioned above, 2) a suggestion of differential mortality in subgroups of the cohort, and 3) the possibility of a substantial lag period before intervention benefit is seen, an extended mortality follow-up was instituted in an effort to clarify the role of one or more of these potential explanations for the results. From this follow-up, data have been analyzed and reported for 10.5 and 16 y postrandomization (6–8)

Although again not significant, CHD mortality in SI men at 10.5 y (202/6428, 31.4 CHD deaths per 1000 men) was 10.6% lower than for UC men (226/6438, 35.1 CHD deaths per 1000 men), and mortality from all causes among SI men was 496/6428 (77.2 deaths per 1000 men), 7.7% lower than mortality from all causes for UC men (537/6438, 83.4 deaths per 1000 men). Although not identified a priori as a primary endpoint of MRFIT, by 10.5 y there was a significant 24.3% lower rate in SI men for acute myocardial infarction ( $P = 0.02$ ), a subcategory accounting for more than half of CHD deaths.

At 16 y, with  $> 2000$  deaths in 12 866 men randomly assigned, rates favorable to the SI group and similar in magnitude to those seen at 10.5 y continued to be observed. Although based on greater numbers of deaths than the earlier rates, neither the 11.4% lower CHD mortality rate for SI men compared with UC men nor the 5.7% lower rate for all-cause mortality seen in SI men was significant; however, the lower rate for acute myocardial infarction in SI men seen at 16 y (20.4%) continued to be significant ( $P = 0.02$ ).  $\square$

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