Body Weight Change, All-Cause Mortality, and Cause-specific Mortality in the Multiple Risk Factor Intervention Trial

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■ *Objective:* To evaluate the relation between weight variability and death in high-risk, middle-aged men participating in the Multiple Risk Factor Intervention Trial (MRFIT).

■ *Design:* Cohort study with 3.8 years of follow-up.

■ *Setting:* Multicenter, collaborative, primary prevention trial conducted at 22 clinical centers in the United States.

■ *Participants:* Men (n = 10 529) who were 35 to 57 years old at baseline and who were in the upper 10% to 15% of risk for coronary heart disease because of smoking, high blood pressure, and elevated cholesterol level. Participants were seen at least annually for 6 to 7 years for medical evaluations in study clinical centers.

■ *Measurements:* Death from cardiovascular disease (228 deaths) and from all causes (380 deaths).

■ *Results:* The primary measure of weight variability was the intrapersonal standard deviation of weight (ISD), which was calculated from measured weights obtained at clinic visits during a 6- to 7-year period. All-cause death rates per 1000 person-years of follow-up across ISD quartiles were 8.28, 8.25, 10.57, and 11.07 from the first to fourth quartiles, respectively. After adjusting for baseline risk factors associated with weight change, the relative risk for all-cause mortality in the fourth compared with the first quartile was 1.64 (95% CI, 1.21 to 2.23). Cardiovascular death and ISD showed a similar pattern. The association between weight change and death was not observed in the heaviest men.

■ *Conclusion:* Greater weight variability was associated with a greater risk for cardiovascular disease and all-cause mortality in some types of high-risk men.

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Weight loss and regain is a common pattern in modern society. Weight gain occurs frequently, as shown by the prevalence of obesity, which is at an all-time high in the United States (1, 2). Weight loss is common, as suggested by the rates of dieting. It has been estimated that approximately 50% of women and 27% of men are dieting at any given time (3). The rates are even higher among young women (4), and several recent case reports have described infants who failed to thrive because they were placed on diets to prevent obesity (5).

Dieting and weight loss are not confined to obese persons. Approximately 25% of adult American women are clinically overweight, but twice as many are dieting (1-3). Because few diets are successful (6), weight loss, weight regain, and repeated weight fluctuation (weight cycling or "yo-yo dieting") occur in many people. If weight variability is associated with negative health outcomes, the public health impact could be substantial because of the number of people affected.

The few studies to examine weight variability report consistent associations between weight change and negative health outcomes (7-9). Weight variability was not associated with death, however, in the Baltimore Longitudinal Study of Aging (10). One weakness of earlier studies has been the infrequent measurement of weight. In the Framingham Heart Study, for example, weights were measured every 2 years. Our study was designed to test the hypothesis that weight change is associated with an increased risk for all-cause and cause-specific mortality in a group of men participating in a longitudinal study for whom frequent weights were available. Data from the Multiple Risk Factor Intervention Trial (MRFIT) permitted a more sensitive measure of weight variability than had been available in previous studies.

Methods

Study Sample

The MRFIT was a randomized, multicenter, primary prevention trial designed to test whether intensive intervention would result in decreased mortality rates from coronary heart disease. Men 35 to 57 years old were screened from 1973 to 1976 at 22 clinical centers in the United States. A total of 361 662 men were screened, and 12 866 who were in the upper 10% to 15% of risk for coronary heart disease (but without clinical evidence of coronary heart disease) were selected for the trial. Men who weighed more than 1.5 times their ideal weight were excluded. Participants were assigned randomly to either a special intervention (SI) or usual care (UC) group. The protocols for selection, randomization, and intervention have been described previously (11, 12). Of those men who were alive at the seventh anniversary of their randomization date (SI group, 6164; UC group, 6171), further exclusions were made if a study

participant missed both his sixth and seventh annual visits (SI group, 432; UC group, 526), if during the trial he had been diagnosed with present or suspected cancer (SI group, 287; UC group, 328), if he had three or fewer recorded weights (SI, 67; UC, 78), or if an error was suspected in a recorded weight (exclusions were based on a recorded weight of 1.96 standard deviations greater or less than the average weight calculated from all other visits and on a recorded weight 15% above or below the weights of the preceding and following weights) (28 men in the SI group and 60 in the UC group). After these exclusions, 10 529 men (5350 in the SI group and 5179 in the UC group) remained for analysis.

Design

This study was designed to provide a chronologic separation of body weight measurement and disease end points. Measured body weights were used for the 6 to 7 years that men were in the intervention phase of the trial. Men in the UC group had weights measured at annual visits, and men in the SI group were weighed every 4 months.

The analysis included deaths that occurred after a seventh annual visit if a participant had attended that visit; otherwise, deaths occurring after the seventh anniversary of randomization were used. Follow-up continued through 31 December 1985 (average, 3.8 years). This procedure separated the temporal sequence of weight change and death. Because disease could cause weight to change and because weight change and disease could be coincidental, this separation was used to avoid confounding created by a causal link between disease and weight change. For this reason, we excluded men who were diagnosed as having cancer.

Weights were measured each time the participant attended a regularly scheduled clinic visit. Procedures for the visits, including methods for measuring weight and ascertaining levels of risk factors, have been described in detail previously (13, 14).

Weight change during the intervention phase of the trial was measured in two ways. The first was the participant's standard deviation of the weight measurements taken at each visit, called the intrapersonal standard deviation of weight (ISD). The ISD is a continuous measure of general weight variability, which increases as the differences in weights across all visits increase. For example, a participant whose weight was 90 kg at the first visit and whose weight declined by 2 kg at each of the next six visits (so that at his last visit his weight was 80 kg) would have an ISD of 3.74. If this participant lost 10 kg between the first and second visits and subsequently gained 2 kg at each of the next five visits, his ISD would be the same. This example shows that the ISD reflects magnitude of variability, not the *type* of weight change. For this reason, a second method was developed to measure the type of weight change within one of five categories:

1) No change was defined as a change of less than 5% from baseline at all visits; 2) steady loss, as a loss greater than or equal to 5% of a previous weight that was not regained; 3) steady gain, as a gain greater than or equal to 5% of a previous weight that was not subsequently lost; 4) cycle with last change a loss, as a loss greater than or equal to 5% of weight that previously had been gained; and 5) cycle with last change a gain, as a gain of 5% or more of weight that previously had been lost.

In both cycle categories, multiple cycles were possible; however, multiple cycles were difficult to detect when only 6 or 7 annual measurements were observed. Many more weight measurements were available for men in the SI group because these participants were invited to attend the clinic (and have their weights measured) at 4-month intervals throughout the trial. To compare results using more frequent measures of weight, some analyses were repeated only for men in the SI group using the weights from all visits to calculate ISD of weight and to note the type of weight change.

Ascertainment of Death

Ascertainment of death was achieved through the U.S. Social Security Administration and from the National Death Index of the National Center for Health Statistics. Death certificates were obtained and coded for underlying cause of death by two trained nosologists with the use of the International Classification of Diseases, Ninth Revision (ICD-9); differences were adjudicated by a third nosologist. Among the 10 529 men included in this analysis, all-cause mortality resulted in 380 deaths, and cardiovascular disease resulted in 228 deaths (ICD-9 390-459).

Statistical Analysis

The association between weight variability and death was evaluated using Cox proportional hazards models, adjusting for baseline covariates that were associated with variability in weight (15). The baseline covariates included age, race, study group, physical activity, body mass index (BMI), diastolic blood pressure, number of cigarettes smoked per day, serum cholesterol level, reported number of alcoholic drinks per week, and use of antihypertensive medications. We also evaluated other models in which change in weight and change in other risk factors (blood pressure, serum cholesterol, cigarettes per day, physical activity, alcohol intake, and antihypertensive drugs) over the intervention phase of the study were added. These findings did not materially change the results, and only data from the former models are presented here. To reduce further the possibility that any association between weight variability and death could be explained by pre-existing disease, analyses were done with the exclusion of men who experienced nonfatal events during the trial. Because results were unchanged compared with analyses using all men, only the results from the latter analyses are reported. (Nonfatal events included nonfatal myocardial infarction, significant serial electrocardiographic changes suggestive of myocardial infarction, stroke, congestive heart failure, renal failure, and digitalis use.)

Because cigarette smoking is associated with both weight and death, analyses were stratified by smoking behavior during the trial to determine whether observed associations between weight variability and mortality could be attributed to changes in smoking behavior. Three smoking groups were created: continuous smokers (those who at every annual visit either reported smoking or had a serum thiocyanate value ≥ 17.2 mmol/L); never smokers (those who at every annual visit both reported not smoking and had a serum thiocyanate value < 17.2 mmol/L); and intermittent smokers (those who would be classified as smokers at some visits and nonsmokers at others, thus including all those whose smoking behavior changed during the trial). Both the continuous smokers and the never smokers had smoking behaviors that did not change during the trial.

Results

After exclusions, 10 529 men remained for analysis. Descriptive information on selected baseline variables and weight change during the trial for these men, stratified by smoking behavior during the trial, is shown in Table 1. The distribution of types of weight change differed by smoking status during the trial. Compared with those whose smoking behavior never changed, intermittent smokers were most likely to gain weight without losing it and were least likely to have no change in weight or to lose weight without regaining it. Compared with the continuous and intermittent smokers, the never smokers were most likely to lose weight without regaining it and were least likely to gain weight without losing it later. Weight cycling was observed in all three groups (40% among intermittent smokers and 33% among continuous and never smokers).

Of the baseline variables considered, several showed significant associations with the ISD (data not shown).

Table 1. Baseline and Weight-Change Characteristics of Men in the Special Intervention and Usual Care Groups by Smoking Patterns during the Multiple Risk Factor Intervention Trial*

Characteristics	All Men (n = 10529)	Continuous Smokers (n = 3740)†	Intermittent Smokers (n = 4014)	Never Smoked (n = 2775)
Baseline				
Age, *y*	46.3	45.4	46.0	48.0
Black, %	7.5	8.0	7.5	6.6
Diastolic blood pressure, *mm Hg*	90.7	88.9	90.6	93.3
Patients using diuretic medication, %	23.0	19.9	23.5	26.4
Serum cholesterol, mmol/L (mg/dL)	6.55 (253.9)	6.40 (246.7)	6.55 (253.0)	6.85 (265.0)
Body mass index‡	27.7	27.2	27.9	28.0
Cigarettes per day, *n*	18.3	32.1	18.2	0.0
Reported alcoholic drinks per week, *n*	12.5	14.3	12.6	9.7
Activity level compared with peer group§	2.9	2.8	2.9	3.0
Special intervention group, %	50.8	43.3	56.9	52.1
Weight changes				
Patients who lost weight without regain, %	18.1	18.4	14.4	23.1
Patients who gained weight without loss, %	19.9	17.8	25.8	14.1
Patients with no change in weight, %	26.2	30.2	20.2	30.0
Patients whose weight cycled, ending with loss, %	10.4	10.4	11.8	8.2
Patients whose weight cycled, ending with gain, %	25.4	23.2	27.8	25.1
Intrapersonal standard deviation of weight, *kg*	2.9	2.7	3.2	2.7

* No differences were seen between men in the special intervention group and those in the usual care group with respect to baseline variables; therefore, data are presented for the two groups combined.

† Continuous smokers were defined as those who at every annual visit attended either reported smoking or had a value of serum thiocyanate greater than or equal to 17.2 mmol/L. Intermittent smokers were defined as those who at at least one annual visit reported not smoking and had a serum thiocyanate value less than 17.2 mmol/L, and at at least another annual visit reported smoking or had a serum thiocyanate value greater than or equal to 17.2 mmol/L. Never smokers were defined as those who at every annual visit attended reported not smoking and had a serum thiocyanate value less than 17.2 mmol/L.

‡ Body mass index calculated as kg/m^2.

§ Activity rating scale in which 1 = least active and 5 = most active.

The ISD of weight was significantly higher in men with a high initial BMI and in those who smoked more cigarettes per day at screen 1 and was marginally associated with higher levels of alcohol consumption. The ISD of weight was lower in older men and in those with higher levels of serum cholesterol and physical activity. The ISD of weight was lower for blacks compared with all other participants and was greater for men in the SI group compared with those in the UC group.

Weight variability as measured by ISD of weight was associated directly with higher mortality rates from cardiovascular disease and from all causes (Table 2). Because of space limitations, data for coronary heart disease are not presented; however, the results were similar to those for cardiovascular disease death in all analyses included here. Adjusted relative risks for death increased steadily from the first through fourth quartiles of ISD of weight, and the regression coefficient for ISD remained statistically significant after adjustment by all variables shown to be associated with ISD of weight. These results were found for men in both the SI and UC groups when weights were observed at annual visits only, and also for men in the SI group when weights were observed at annual visits and at the 4- and 8-month visits.

The ISD of weight is a measure of general weight variability, including both progressive and cyclical changes in weight. Table 3 shows the association between death and patterns of weight change during the trial for men in both study groups using data from annual visits and for men in the SI group using data from annual visits plus those from 4- and 8-month visits. In all cases examined, men whose weights remained stable were at the lowest adjusted risk for death compared with those whose weight changed. Both unadjusted rates and adjusted relative risks for death were higher for those with a sustained weight loss compared with those with a sustained weight gain. No uniform pattern of higher or lower mortality rates was seen when we compared men whose weight cycled with those whose weight changed only once or when we compared weight cyclers having final losses of weight with weight cyclers having final gains in weight. When we examined data from men in both study groups combined, the number of weight-change cycles was significantly associated with higher mortality rates (after adjustment for baseline variables and for a steady loss and a steady gain in weight).

Because variability in weight was associated with smoking habits, additional analyses were done to determine whether the association between weight variability and death depended on participants' smoking habits during the trial. As can be seen in Table 4, a statistically significant positive association was seen between all-cause mortality and ISD of weight as a continuous variable for all three smoking groups, and the magnitude of the coefficient for ISD of weight was virtually the same in all groups. Unadjusted rates and adjusted relative risks for death by quartile of ISD were distributed somewhat erratically, however, although mortality rates in the highest ISD quartile always exceeded those in the lowest.

Table 2. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups of the Multiple Risk Factor Intervention Trial by Quartiles of Intrapersonal Standard Deviation of Weight*

Variable	Mortality from Cardiovascular Disease				All-Cause Mortality		
Quartiles of ISD	Men	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡
kg	*n*	*n*			*n*		
SI and UC Men§							
ISD < 1.79 (average, 1.36)	2631	49	4.89	1.00	83	8.28	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	2632	52	5.23	1.15 (0.77 to 1.70)	82	8.25	1.04 (0.77 to 1.41)
2.54 < ISD ≤ 3.62 (average, 3.02)	2634	59	5.94	1.47 (0.99 to 2.16)	105	10.57	1.46 (1.09 to 1.96)
ISD > 3.62 (average, 5.17)	2632	68	6.84	1.85 (1.25 to 2.75)	110	11.07	1.64 (1.21 to 2.23)
Coefficient for ISD of weight		0.138			0.123		
P value for coefficient		<0.001			<0.001		
SI Men§							
ISD < 1.88 (average, 1.53)	1330	19	3.75	1.00	35	6.92	1.00
1.88 < ISD ≤ 2.51 (average, 2.19)	1331	20	3.93	1.20 (0.64 to 2.26)	34	6.69	1.04 (0.65 to 1.68)
2.51 < ISD ≤ 3.38 (average, 2.92)	1331	26	5.21	1.76 (0.96 to 3.23)	49	9.82	1.64 (1.05 to 2.57)
ISD > 3.38 (average, 4.72)	1330	33	6.57	2.60 (1.41 to 4.79)	51	10.16	1.88 (1.18 to 3.01)
Coefficient for ISD of weight		0.209			0.164		
P value for coefficient		0.001			0.002		

* ISD = intrapersonal standard deviation (of weight); SI = special intervention; UC = usual care.
† Calculated as number of deaths per 1000 person-years.
‡ Models adjusted for age, race, inclusion in the SI group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, body mass index, number of cigarettes smoked per day, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.
§ Analyses for all men based on data from annual visits. Analyses for SI men based on data from annual visits and from 4- and 8-month visits.

Table 5 shows the association between death and types of weight change for the three smoking groups. Weight cycling showed the strongest statistically significant association with death in the continuous smokers, although the magnitudes of the coefficients were similar to those for never smokers, who generally had lower death rates. Except for the intermittent smokers, who had a sustained weight gain, mortality rates were the lowest among men with stable weights, regardless of smoking behavior. Among continuous smokers, little difference in mortality rates was seen between men who had a sustained weight loss and those who had a sustained weight gain.

The strongest associations between ISD of weight and death were seen in men in the lowest two tertiles of baseline BMI (Table 6). For the heaviest men at base-

Table 3. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups of the Multiple Risk Factor Intervention Trial by Type of Weight Change*

Type of Weight Change	Cardiovascular Disease Mortality				All-Cause Mortality		
	Men	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡
	n	*n*			*n*		
SI and UC Men§							
No change	2760	43	4.12	1.00	75	7.18	1.00
Lose only	1908	45	6.19	1.61 (1.05 to 2.45)	79	10.87	1.62 (1.18 to 2.23)
Gain only	2092	39	5.01	1.28 (0.83 to 1.98)	67	8.60	1.20 (0.86 to 1.67)
Cycle, lose at end	1090	29	7.07	1.73 (1.08 to 2.79)	54	13.17	1.76 (1.23 to 2.50)
Cycle, gain at end	2679	72	7.05	1.89 (1.29 to 2.78)	105	10.28	1.53 (1.13 to 2.07)
Coefficient for the number of weight-change cycles		0.379			0.304		
P value for coefficient		0.006			0.005		
SI Men§							
No change	654	6	2.42	1.00	12	4.84	1.00
Lose only	601	19	8.31	3.42 (1.36 to 8.60)	31	13.56	2.87 (1.47 to 5.61)
Gain only	708	12	4.52	1.83 (0.68 to 4.91)	20	7.54	1.50 (0.73 to 3.09)
Cycle, lose at end	1109	21	4.99	2.05 (0.82 to 5.10)	39	9.27	1.85 (0.97 to 3.55)
Cycle, gain at end	2250	40	4.69	2.05 (0.87 to 4.87)	67	7.85	1.69 (0.91 to 3.14)
Coefficient for the number of weight-change cycles		0.218			0.201		
P value for coefficient		0.115			0.056		

* SI = special intervention; UC = usual care.
† Calculated as number of deaths per 1000 person-years.
‡ Models adjusted for age, race, inclusion in SI group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, body mass index, number of cigarettes smoked per day, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.
§ Analyses for all men based on data from annual visits. Analyses for SI men based on data from annual visits and from 4- and 8-month visits.

Table 4. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups by Quartiles of Intrapersonal Standard Deviation of Weight and Smoking Patterns During the Multiple Risk Factor Intervention Trial*

Quartiles by Smoking Status	Cardiovascular Disease Mortality				All-Cause Mortality		
	Men	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡
	n	*n*			*n*		
Continuous smokers							
ISD < 1.79 (average, 1.36)	1082	21	5.16	1.00	43	10.56	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	988	26	7.11	1.41 (0.79 to 2.52)	42	11.49	1.09 (0.71 to 1.67)
2.54 < ISD ≤ 3.62 (average, 3.02)	877	24	7.41	1.64 (0.90 to 2.97)	46	14.20	1.50 (0.98 to 2.29)
ISD > 3.62 (average, 5.17)	793	31	10.56	2.55 (1.41 to 4.62)	51	17.37	1.94 (1.26 to 3.00)
Coefficient for ISD of weight		0.163			0.132		
P value for coefficient		0.001			0.001		
Intermittent smokers							
ISD < 1.79 (average, 1.36)	725	16	5.79	1.00	21	7.60	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	937	11	3.09	0.57 (0.26 to 1.23)	18	5.06	0.72 (0.38 to 1.36)
2.54 < ISD ≤ 3.62 (average, 3.02)	1068	24	5.94	1.20 (0.63 to 2.29)	38	9.41	1.41 (0.81 to 2.43)
ISD > 3.62 (average, 5.17)	1284	25	5.15	1.16 (0.59 to 2.28)	44	9.07	1.49 (0.85 to 2.60)
Coefficient for ISD of weight		0.117			0.148		
P value for coefficient		0.069			0.002		
Never smoked							
ISD < 1.79 (average, 1.36)	824	12	3.77	1.00	19	5.96	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	707	15	5.51	1.58 (0.73 to 3.41)	22	8.08	1.48 (0.79 to 2.75)
2.54 < ISD ≤ 3.62 (average, 3.02)	689	11	4.15	1.28 (0.54 to 3.04)	21	7.92	1.66 (0.86 to 3.20)
ISD > 3.62 (average, 5.17)	555	12	5.57	1.97 (0.81 to 4.82)	15	6.97	1.75 (0.83 to 3.70)
Coefficient for ISD of weight		0.100			0.126		
P value for coefficient		0.143			0.046		

* ISD = intrapersonal standard deviation (of weight).
† Calculated as number of deaths per 1000 person-years.
‡ Models adjusted for age, race, inclusion in the intervention group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, body mass index, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.

line, no statistically significant association was seen between weight variability and death. The association between number of weight cycles and death was limited to the lowest tertile of baseline BMI (Table 7). The adjusted relative risks for weight change categories were higher than the "no change" group, but the 95% confidence intervals included 1.0 in the two highest tertiles.

To examine the possibility that preclinical illness might cause both weight change and death, the associations were examined using lengthened time intervals between the determination of weight variability and subsequent death. Two analyses were done. First, ISD was calculated through the sixth year, with mortality rate determined after the eighth anniversary of randomization. A second analysis used weights through 5 years and death after the seventh anniversary. These analyses adjusted for age, race, study group, and baseline coronary heart disease risk factors. The ISD of weight retained a statistically significant association with all-cause mortality when a minimum of 2 years elapsed between the final recorded weight and the beginning of mortality follow-up. The findings were similar for men in the SI group, the total study group, and across smoking habit strata.

Discussion

Our results indicate that MRFIT participants who had changes in body weight during the intervention phase of the trial were more likely to die during post-trial follow-up than were men whose weights remained stable. One of the strengths of this study is that weights were measured more frequently than in previous studies (especially among men in the SI group), which should result in a more precise index of weight variability. Higher ISDs were associated with higher all-cause, cardiovascular disease, and coronary heart disease mortality rates. The association between ISD and death was noted in both SI and UC groups. The overall impression of these analyses suggests a harmful effect of weight variability on health, a finding that is consistent with most previous studies using different samples and methods (7-9).

The ISD measures variability in the weights recorded at clinic visits during the trial but does not account for the sequence of weights observed for each man. Another way to assess weight variability is to characterize relevant patterns of weight change; that is, to develop weight-change categories. The weight-change analyses reported here sorted participants into groups with stable weights throughout the trial, in which participants never gained or lost as much as 5% of body weight; lose-only and gain-only groups, in which the men lost or gained at least 5% of body weight; and the weight cyclers. A single cycle in the analyses done for this report consisted of a gain (or loss) greater than or equal to 5% of body weight followed by a loss (or gain) greater than or equal to 5%. The weight-change category analyses showed that the group with stable weights had the lowest mortality rates. The lose-only and gain-only groups had somewhat higher mortality rates than did the stable men, and the increased risk was greater in the steady-loss group than in the steady-gain group. Men whose

Table 5. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups by Type of Weight Change and Smoking Pattern during the Multiple Risk Factor Intervention Trial

Weight Change and Smoking Status	Cardiovascular Disease Mortality				All-Cause Mortality		
	Men	Deaths	Death Rate*	Adjusted Relative Risk (95% CI)†	Deaths	Death Rate*	Adjusted Relative Risk (95% CI)†
	n	*n*			*n*		
Continuous smokers							
No change	1129	18	4.26	1.00	37	8.76	1.00
Lose only	690	18	6.98	1.56 (0.81 to 3.03)	34	13.18	1.48 (0.92 to 2.38)
Gain only	665	20	8.22	2.12 (1.12 to 4.03)	31	12.74	1.53 (0.95 to 2.48)
Cycle, lose at end	390	13	9.17	2.22 (1.08 to 4.57)	32	22.57	2.52 (1.56 to 4.07)
Cycle, gain at end	866	33	10.16	2.65 (1.48 to 4.76)	48	14.78	1.80 (1.16 to 2.78)
Coefficient for the number of weight-change cycles		0.537			0.470		
P value for coefficient		0.010			0.002		
Intermittent smokers							
No change	812	15	4.88	1.00	21	6.83	1.00
Lose only	577	12	5.49	1.25 (0.58 to 2.71)	24	10.98	1.80 (0.99 to 3.26)
Gain only	1036	15	3.87	0.73 (0.35 to 1.53)	23	5.93	0.80 (0.44 to 1.47)
Cycle, lose at end	473	9	4.97	1.04 (0.45 to 2.41)	15	8.29	1.16 (0.59 to 2.28)
Cycle, gain at end	1116	25	5.87	1.41 (0.74 to 2.71)	38	8.92	1.43 (0.83 to 2.46)
Coefficient for the number of weight-change cycles		0.189			0.199		
P value for coefficient		0.438			0.318		
Never smoked							
No change	819	10	3.18	1.00	17	5.40	1.00
Lose only	641	15	5.98	1.81 (0.80 to 4.12)	21	8.38	1.57 (0.81 to 3.03)
Gain only	391	4	2.70	0.94 (0.29 to 3.03)	13	8.79	1.78 (0.86 to 3.70)
Cycle, lose at end	227	7	8.02	2.36 (0.87 to 6.42)	7	8.02	1.54 (0.63 to 3.79)
Cycle, gain at end	697	14	5.17	1.72 (0.74 to 4.00)	19	7.02	1.45 (0.73 to 2.86)
Coefficient for the number of weight-change cycles		0.548			0.327		
P value for coefficient		0.071			0.204		

* Rates of death calculated as number of deaths per thousand person-years.

† Models adjusted for age, race, inclusion in the intervention group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, body mass index, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.

weights cycled also were more likely to die during follow-up than were the men with stable weights.

Stratified analyses by tertile of baseline BMI indicated that the effect of ISD on mortality rate was restricted to men in the first and second tertiles. The mechanism for these findings is unknown but could be related to confounding by nonfatal disease or smoking behavior in the leaner subgroups of men. A doubling of risk for all-cause mortality was noted in the leanest men when we compared those having the largest amount of weight change with those having the least (*see* Table 6). No clear trend of increased risk was seen across quartiles of ISD in the heaviest men (tertile three of baseline BMI).

As seen in Table 7, a statistically significant association between death and weight cycling was exhibited only by men in the lowest tertile of baseline BMI. This observation raises two questions: Why did these leaner men cycle, and why would cycling be associated with death for them but not for the heavier participants?

To answer the first question, we first note that weight change among the leanest men was less likely to occur than weight change among initially heavier men. In the first BMI tertile, 31.7% of the men showed no change in weight, whereas this percentage decreased to 26.7% and 20.1% in the second and third BMI tertiles, respectively. Of those in the first BMI tertile who did show a change, the largest number ($n = 798$) had a steady gain, a finding that may be attributable either to smoking cessation or reduction in number of cigarettes smoked, given that 87.3% of these men were either continuous or intermittent smokers (data not shown). By contrast, only 73.6% of men in the entire study group were continuous or intermittent smokers. Weight cycling was exhibited by 29.6% of the men in the first BMI tertile, 33.5% in the second tertile, and 44.4% in the third tertile. Thus cycling was associated with initially heavy men.

Among the 29.6% of men in the first BMI tertile who did cycle, a slightly higher percentage used diuretics intermittently throughout the trial, and a slightly higher percentage smoked cigarettes intermittently throughout the trial. These differences were not statistically significant and were also observed in the upper two tertiles of BMI (data not shown).

Nonfatal events were experienced by 169 of the men in the first BMI tertile; 67 (39.6%) of these men cycled in weight compared with 29.6% of all men in this tertile, a statistically significant difference. In the second BMI tertile, men who experienced nonfatal events cycled at a rate of 36.4% compared with 33.5% for all men in this group, and, in the third BMI tertile, men who experienced nonfatal events cycled at a rate of 57.7% compared with 44.4% of all men in this group.

The BMI tertile-specific analyses suggest that weight variability increases risk in leaner men but has a limited effect in heavier men. These findings emphasize that

Table 6. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups by Quartiles of Intrapersonal Standard Deviation of Weight and Baseline Body Mass Index*

Quartiles of ISD (kg) and Baseline BMI	Cardiovascular Disease Mortality				All-Cause Mortality		
	Men	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡
	n	*n*			*n*		
BMI < 26.08 (average, 24.20)							
ISD < 1.79 (average, 1.36)	1337	32	6.26	1.00	48	9.40	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	1019	33	8.68	1.38 (0.85 to 2.27)	48	12.62	1.35 (0.90 to 2.02)
2.54 < ISD ≤ 3.62 (average, 3.02)	712	26	9.80	1.62 (0.96 to 2.74)	42	15.83	1.71 (1.12 to 2.60)
ISD > 3.62 (average, 5.17)	444	20	12.18	2.04 (1.15 to 3.64)	31	18.89	2.06 (1.29 to 3.29)
Coefficient for ISD of weight		0.168			0.181		
P value for coefficient		0.005			< 0.001		
26.08 < BMI ≤ 28.82 (average, 27.40)							
ISD < 1.79 (average, 1.36)	866	7	2.12	1.00	21	6.36	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	969	8	2.16	1.16 (0.42 to 3.22)	20	5.40	0.91 (0.49 to 1.69)
2.54 < ISD ≤ 3.62 (average, 3.02)	944	17	4.75	2.62 (1.07 to 6.41)	32	8.94	1.53 (0.88 to 2.68)
ISD > 3.62 (average, 5.17)	731	16	5.83	3.20 (1.27 to 8.06)	26	9.47	1.55 (0.85 to 2.80)
Coefficient for ISD of weight		0.205			0.146		
P value for coefficient		0.068			0.002		
BMI > 28.82 (average, 31.49)							
ISD < 1.79 (average, 1.36)	428	10	6.22	1.00	14	8.71	1.00
1.79 < ISD ≤ 2.54 (average, 2.16)	644	11	4.53	0.79 (0.33 to 1.86)	14	5.77	0.73 (0.35 to 1.54)
2.54 < ISD ≤ 3.62 (average, 3.02)	978	16	4.33	0.77 (0.35 to 1.73)	31	8.38	1.03 (0.54 to 1.95)
ISD > 3.62 (average, 5.17)	1457	32	5.76	1.03 (0.49 to 2.17)	53	9.54	1.20 (0.65 to 2.22)
Coefficient for ISD of weight		0.048			0.059		
P value for coefficient		0.417			0.202		

* BMI = body mass index (kg/m^2); ISD = intrapersonal standard deviation (of weight).
† Rates of death calculated as number of deaths per thousand person-years.
‡ Models adjusted for age, race, inclusion in the intervention group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, number of cigarettes smoked per day, body mass index, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.

little concern should exist about recommending weight reduction in high-risk men who are overweight.

Our results do not appear to be confounded by other risk factors or clinical variables. A major concern was the possibility that disease might cause gain or loss of weight. This possibility is lessened by the study design, which temporally separates determination of weight variability from subsequent death, and by analyses that excluded men who developed nonfatal disease during the trial. These additional analyses did not significantly alter the primary results.

Several limitations must be acknowledged when interpreting these results. The MRFIT was not a weight-loss trial, although multiple interventions on smoking, nutrition, and blood pressure can affect weight, as can changes in physical activity. Thus, the observed weight changes may have been markers for other changes that were associated with death. This seems unlikely because the interventions used in the study appear to reduce, not increase, risk (16). This concern is further addressed by the adjustment of models for the association between weight change and death by other factors known to be associated with weight change. Change in smoking habits could have affected both death and weight fluctuation, but separate analyses in smoking change groups showed similar associations between weight change and death. Additional models were developed in which change in other risk factors and clinical variables were added as covariates during the course of the trial (data not shown), and these analyses did not change the relation of weight variability to death. The results also are corroborated by data from the Framingham study, in which multiple interventions were not done (8). Thus, it seems unlikely that risk factor interventions in the MRFIT were responsible for the observed relation between weight variability and death. Ample evidence supports the positive health effects of most of these interventions, and our results suggest that such treatments are beneficial.

Men who lost 5% or more of their baseline weight and maintained the loss throughout the trial were at increased risk for death compared with men who had stable weights. This finding was seen in all men when annual weight measurements were used in the calculations and in men in the SI group when all weight measurements were used. This finding was consistent across smoking groups. Weight loss in these men at high risk for coronary heart disease might be expected to reduce risk, but that was not the case. Similar findings are reported from other studies (17, 18).

The biological mechanisms whereby weight change increases mortality risk are not clear. It has been hypothesized that repeated bouts of dieting and weight fluctuation may depress metabolic rate, increase fat deposition, and increase dietary preference for fat (19, 20). Other studies, however, do not support these hypotheses (21-23). More basic research is needed to help interpret the epidemiologic findings.

Our data support the conclusion that weight change is associated with increased mortality risk. It is unclear whether weight change in these men was due to voluntary attempts at weight loss or to other factors. Unfortunately, the available data did not allow us to determine whether weight change was voluntary. Information on dietary at-

Table 7. Cardiovascular and Total Mortality for Men in the Special Intervention and Usual Care Groups by Type of Weight Change and Baseline Body Mass Index*

Type of Weight Change and Baseline BMI	Cardiovascular Disease Mortality				All-Cause Mortality		
	Men	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡	Deaths	Death Rate†	Adjusted Relative Risk (95% CI)‡
	n	*n*			*n*		
BMI < 26.08 (average, 24.20)							
No change	1115	24	5.69	1.00	40	9.48	1.00
Lose only	562	19	8.91	1.59 (0.86 to 2.93)	28	13.12	1.41 (0.86 to 2.30)
Gain only	798	16	5.37	0.97 (0.51 to 1.85)	28	9.41	0.97 (0.60 to 1.59)
Cycle, lose at end	378	19	13.60	2.38 (1.29 to 4.40)	31	22.20	2.15 (1.33 to 3.46)
Cycle, gain at end	659	33	13.30	2.24 (1.32 to 3.82)	42	16.93	1.70 (1.10 to 2.64)
Coefficient for the number of weight change cycles		0.572			0.407		
P value for coefficient		<0.001			0.002		
26.08 < BMI ≤ 28.82 (average, 27.40)							
No change	939	7	1.96	1.00	18	5.03	1.00
Lose only	709	14	5.11	2.95 (1.17 to 7.42)	25	9.12	2.02 (1.09 to 3.74)
Gain only	686	12	4.71	2.39 (0.92 to 6.20)	20	7.85	1.47 (0.79 to 2.82)
Cycle, lose at end	296	2	1.79	1.13 (0.23 to 5.49)	9	8.07	1.66 (0.74 to 3.72)
Cycle, gain at end	880	13	3.88	2.06 (0.81 to 5.23)	27	8.05	1.60 (0.88 to 2.93)
Coefficient for the number of weight change cycles		−0.154			0.152		
P value for coefficient		0.589			0.395		
BMI > 28.82 (average, 31.49)							
No change	706	12	4.52	1.00	17	6.41	1.00
Lose only	637	12	5.01	1.11 (0.49 to 2.49)	26	10.85	1.62 (0.87 to 3.02)
Gain only	608	11	4.85	1.26 (0.55 to 2.88)	19	8.38	1.45 (0.75 to 2.82)
Cycle, lose at end	416	8	5.04	1.05 (0.42 to 2.61)	14	8.81	1.26 (0.61 to 2.59)
Cycle, gain at end	1140	26	5.93	1.34 (0.66 to 2.70)	36	8.22	1.27 (0.70 to 2.29)
Coefficient for the number of weight change cycles		0.061			−0.096		
P value for coefficient		0.758			0.552		

* BMI = body mass index (kg/m^2).
† Calculated as number of deaths per 1000 person-years.
‡ Models adjusted for age, race, inclusion in the intervention group, and baseline values of diastolic blood pressure, diuretic use, serum cholesterol, number of cigarettes smoked per day, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group.

tempts at weight loss would have been helpful in this regard. Analyses were adjusted for major potential contributors to involuntary weight loss such as morbidity, changes in smoking status, and diuretic use. The relation between weight change and mortality remained after all such adjustments. The increased risk of weight change was restricted primarily to men in the first BMI tertile; therefore, it continues to seem reasonable to recommend weight loss in high-risk, overweight men.

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