THE EFFECT OF WEIGHT CYCLING ON BLOOD LIPIDS AND BLOOD PRESSURE IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL SPECIAL INTERVENTION POPULATION

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ABSTRACT

THE EFFECT OF WEIGHT CYCLING ON BLOOD LIPIDS AND BLOOD PRESSURE IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT) SPECIAL INTERVENTION POPULATION

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The purpose of this study was to assess whether increases in mortality associated with weight cycling in a number of populations might be mediated by the traditional cardiovascular risk factors of total cholesterol, high-density lipoprotein cholesterol (HDL), the ratio of total cholesterol to HDL and blood pressure. The study population consisted of 6,000 men at high risk for heart disease in the Special Intervention group of the MRFIT, selected because the data set includes weight, cholesterol, and blood pressure measured every 4 months over a 7-year period, as well as documentation of other cardiovascular disease risk factors. Three measures of weight cycling were defined: (1) the number of weight cycles, defined as the number of times an individual lost and subsequently regained at least 5% of his baseline weight; (2) the standard error of the estimate (SEE) of the regression of weight on time for each individual, (3) a combination of number of cycles and SEE, reflecting the number and size of cycles. A number of analysis of covariance and stepwise regression models were developed, with the three measures of weight cycling as predictor variables, changes in the four risk factors as outcome variables and control for

all factors statistically associated with the outcomes. The hypothesis that men who weight cycled experienced smaller improvements in their blood lipids and blood pressure than those who did not cycle was not supported. If weight cycling is causing increased mortality in middle aged men at high risk for heart disease, it does not appear to be having this effect because of adverse effects on blood lipids or blood pressure.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

ANOVA - analysis of variance
ANCOVA - analysis of covariance
ACTH - adrenocorticotropic hormone
BMI - body mass index = kg/m^2
BT - behavioral therapy
CV - coefficient of variability = s.d./mean
CVD - cardiovascular disease
dl - deciliter
g - grams
HDL - high density lipoproteins
kg - kilograms
lb- pounds
LDL - low density lipoproteins
LTPA - leisure time physical activity
m - meters
mg - milligrams
min - minutes
mm Hg - millimeters of mercury
mg/dl - milligrams per deciliter
MRFIT - Multiple Risk Factor Intervention Trial
n - number
NHLBI - National Heart, Lung and Blood Institute
n.s. - not significant
P:S Ratio - ratio of polyunsaturated to saturated fats
SEE - standard error of the estimate for the regression of each subject's weight on time
SI - Special Intervention
s.d. - standard deviation
UC - Usual Care
VLCD - very low calorie diet
VLDL - very low density lipoproteins
wt - weight

INTRODUCTION

Aims of Research: The aims of the work described here were to determine the effect of weight cycling on the cardiovascular disease (CVD) risk factors of blood lipids and blood pressure, using the rich data set of the Multiple Risk Factor Intervention Trial (MRFIT). It has already been demonstrated in the MRFIT population[1] and in several other populations[2, 3, 4] that weight cycling is associated with increased risk of mortality. This association does not establish that weight cycling causes increased mortality. No credible explanation has been advanced which could link weight cycling causally to increased cardiovascular mortality. This study takes a step toward clarifying whether weight changes are causally related by looking at intermediate outcomes associated with heart disease – blood lipids and blood pressure.

The specific hypothesis explored in this research is that men who experienced weight cycling over the 6–year course of the MRFIT realized smaller improvements in the CVD risk factors of total serum cholesterol concentration, high density lipoprotein (HDL) concentrations, the ratio of total plasma cholesterol to HDL, and diastolic blood pressure, compared with men who did not weight cycle.

Relevance of the Research to National Health Goals: An important

national health goal is to reduce cardiovascular disease, the leading cause of death in the United States.[5] Inasmuch as obesity is a major risk factor for heart disease and affects 34 million American adults (including 12.5 million severely overweight individuals),[6] long-term health implications for obesity intervention must be clearly understood.

Until very recently, conventional wisdom and scientific recommendations[7] were to strongly promote weight loss for essentially everyone whose body weight was above average. The general public seems to be taking this conventional wisdom to heart: 40% of women and 20% of men are dieting at any one time,[8] including many who are not overweight by any objective standard. Recent research has led many thoughtful health professionals to question whether weight loss, *per se*, is an appropriate recommendation for most overweight individuals. Although weight loss improves cholesterol and blood pressure in the short run,[9,10] the vast majority of people who lose weight regain it.[11,12] Weight gain is associated with worsening of blood lipid profiles and blood pressure,[10] and, as cited above, the increased weight variability caused by weight loss and regain has been shown in several studies to increase the risk of mortality. Not only has weight cycling been shown to be associated with increased CVD mortality, weight loss has also been associated with increased mortality[1,2,4,13,14,15,16,17,18] in almost every published analysis of weight change and mortality.

If weight loss (and its almost inevitable weight regain) are, by some mechanism, increasing health risk rather than decreasing it, national health

goals related to decreasing the incidence of obesity may have to be revised. The National Task Force on the Prevention and Treatment of Obesity recently published a review acknowledging potential health risks from weight cycling.[19] Although the Task Force did not recommend against weight loss *per se*, its recommendations were very conservative compared to earlier consensus documents, calling for "*moderate* weight loss" for "*significantly* obese patients." If further research verifies increased health risk from weight loss and regain, future recommendations for obesity treatment are likely to be even more conservative.

LITERATURE REVIEW

Weight and Health

Weight and Health Risk Factors: There is universal recognition that extreme levels of adiposity are associated with increased risk of early mortality and of various medical condititons. Pi-Sunyer summarized current understanding of these risks in an extensively documented 1993 review.[20] According to Dr. Pi-Sunyer, obesity is associated with insulin resistance, diabetes mellitus, hypertension, hypertriglyceridemia, decreased levels of high-density lipoprotein cholesterol and increased levels of low-density lipoprotein cholesterol. Obesity is also associated with gallbladder disease and some forms of cancer as well as sleep apnea, chronic hypoxia and hypercapnia, and degenerative joint disease.

Weight and Mortality: Obesity is an independent risk factor for death from coronary heart disease, however, there is controversy about the precise relationship between weight and mortality. Large prospective population studies in which the relationship between weight at some time and subsequent mortality have been quantified produce conflicting findings.

Manson et al.[21] reviewed 25 major prospective studies on weight and longevity, most of which reported J-shaped or U-shaped weight-mortality curves.

They concluded that each of the studies had at least one of three major biases: (1) failure to control for the effects of smoking, which would show excess mortality at lower weights that should be explained by smoking's impact on health, erroneously yielding a J-shaped mortality curve; (2) inappropriate control for biologic effects of obesity. This means that researchers eliminated from the analysis individuals with diabetes or hypertension, conditions which may be caused by weight. In eliminating such individuals from analysis, negative health consequences of obesity are not reflected in the plot, yielding a flattened curve; (3) failure to control for weight loss due to subclinical disease. This would also show excess mortality at lower weights, actually attributable to undiagnosed diseases causing weight loss. This bias would also erroneously produce a J-shaped mortality curve.

The authors believed that the presence of these biases leads to systematic underestimation of the detrimental impact of obesity on premature mortality. They suggested the true relationship between weight and mortality is linear. In an analysis of mortality among 15,195 of the women in the Nurses Health Study,[22] this same group demonstrated that when pertinent confounding variables were controlled for, a linear relationship was found between BMI at age 30-55 and subsequent mortality. A similar linear curve was observed in the 26-year mortality study of Seventh Day Adventists.[23] The Adventists could be considered an ideal population for epidemiological study because they eat a relatively low-fat vegetarian diet, and do not use tobacco, drink alcohol, or take caffeine-containing beverages.

In a more recent review which took into account the concerns expressed by Manson et al.,[21] Kushner[24] reported that, in some studies, weight is found to have no association with mortality. In a few studies, a linear, dose–response relationship is reported, such that as weight increases, risk of mortality increases. In most studies, the weight–mortality curves are found to be J–shaped or U–shaped, with increased mortality present at both extremes of weight.

There is still lively debate in the health community about how to define an "ideal body weight." The issue is made more complex by recent evidence, reviewed below, that weight loss and weight cycling may increase risk of mortality.

Weight Loss and Health

Until very recently, it has been believed without question that, since being overweight is associated with increased mortality, losing weight would improve an individual's prospects for a long, healthy life. There is now evidence, described below, that, despite the fact that weight loss improves known risk factors for mortality in the short run, weight loss may ultimately increase the risk of early mortality.

Weight Loss and CVD Risk Factors: There is no question that weight loss, in the short run, is associated with improvements in CVD risk factors. This was demonstrated vividly in Ashley and Kannel's landmark analysis of Framingham data.[10] Using weight and health data on 5,209 adults, it was clearly demonstrated that, as weight increased, atherogenic traits (blood pressure, cholesterol, uric acid, and triglycerides) all worsened. When weight

decreased, the same atherogenic traits improved. The rate of improvements in atherogenic traits with weight loss was greater than the rate of worsening in traits with weight gain.

More recently, Goldstein[9] conducted a thorough review of the medical effects of modest weight reduction (loss of approximately 10% or less) in patients with obesity-related complications. These clinical studies demonstrated that for obese patients with non-insulin dependent diabetes mellitus (14 studies), hypertension (13 studies), or hyperlipidemia (6 studies), modest weight reduction appeared to improve glycemic control, reduce blood pressure, and reduce cholesterol levels.

One notable exception to the general finding that weight loss reduces risk factors was reported by Phinney et al.,[25] who found a consistent hypercholesterolemia in patients with major weight loss. The condition was transient, however, resolving when weight stabilized.

Whether weight loss itself causes the improvements in the risk profile is not altogether clear. While individuals are losing weight, they are also modifying their diets and often modifying their exercise patterns. It is known that exercise alone, and dietary change alone, without weight loss, can cause reduction in blood pressure and cholesterol concentrations. The independent effect of weight loss is seldom clear. Nevertheless, a large body of research consistently demonstrates that weight loss is associated with reductions in health risk factors in the short run.

Weight Loss and Mortality: In contrast to the effect of weight loss on risk

factors for mortality, there is evidence to suggest that weight loss may be associated with increased rather than decreased mortality. This possibility has been seriously considered only since 1992, with publication of two critical reappraisals of the literature available on weight change and mortality,[26,14] plus the publication of new data analyses.

Critical Reappraisals of Literature of Weight Change and Mortality: In preparation for the 1992 Technology Assessment Conference on Methods of Voluntary Weight Loss and Control, sponsored by the National Institutes of Health, the existing body of research on weight change and mortality was systematically re-examined and summarized in two papers. The first critical reappraisal was presented by Williamson and Pamuk,[26] who reviewed six observational epidemiologic studies published between 1951 and 1990 in which weight loss had been found to be predictive of greater longevity.

Each of the studies was found to have serious flaws which weakened or negated the conclusion that weight loss enhanced longevity. The most credible studies were those based on actuarial data.[27, 28, 29] In these studies, life insurance companies studied policy holders who were required to pay higher premiums because they were overweight. Some of these individuals later lost weight, and were granted lower premiums. The slenderized policy holders were compared with those who were never granted premium reductions, and were found to have lower mortality rates. These studies did not provide information about the amount and duration of the weight loss or levels of obesity in the weight loss and comparison groups.

Williamson and Pamuk [26] considered each of the other four studies to be seriously flawed. Although each of the studies reported that weight loss was associated with increased survival, two of the studies found that mortality actually increased among subgroups of persons who lost weight (the Cancer Prevention Study I [30] and the British Regional Heart Study [31]), and the other two did not provide data to support the finding (the 1979 Build Study[32] and the Aberdeen Diabetic Study [33]). The Aberdeen Diabetic Study also contained a major mathematical error which weakened its author's conclusions that weight loss predicted lower mortality. (Williamson and Pamuk pointed out that the authors had failed to square the slope coefficient in their interpretation of their regression findings, so that the effect of weight loss was overestimated. The .036 years of increased survival that the authors reported was actually only 0.0013 years.)

Taken as a whole, Williamson and Pamuk [26] concluded that the evidence from these six studies that weight loss in obese persons increases longevity was equivocal. None of the six studies provides any information on the type of weight loss methods used by the subjects. Although cycles of weight loss and regain could be expected to be common among overweight individuals, none of the studies included information about history of weight cycling or average lifetime weight compared to weight at the two points in time measurements were taken.

The remaining published research on weight change and mortality not addressed by Williamson and Pamuk was critically reviewed in a second paper

at the Technology Assessment Conference by Andres et al,[14] who re-examined published studies to determine which weight changes were associated with the lowest mortality rate. In each of the twelve studies reviewed, weight change was computed using weight at two time points during adult life. Participants were subsequently followed for a period of years to quantify the mortality rate. The twelve studies included very diverse populations (seven U.S. populations and four European groups). The segments of adult life during which weight change was documented were variable, ranging from two points in early adulthood to two points in later life. The duration of the weight change period ranged from 3.7 years to several decades. The period of follow-up varied from 8-22 years. In every study the effect of pre-existing illness on weight was addressed in some way. A variety of techniques was used to assess weight change, and methods of data analysis differed.

Despite the variety of approaches used, the results were largely similar with respect to the effect of weight loss on mortality. "Mild to moderate weight loss" was associated with increased mortality in ten of the studies. Mortality risk was decreased by weight loss in only one study. "Mild to moderate weight loss" was defined differently in each study, but typically involved loss of 10% or more, loss of >1.13 BMI units, or loss of 5.5-13.6 kg. This analysis is summarized in Table 1.

Table 1 – Association of Mild to Moderate Weight Loss with All-Cause Mortality Reported by Andres et al.[14]

Population / Study	High Mortality	No Effect on Mortality	Low Mortality
Paris Civil Servants [34]	Males		
Dutch Longitudinal Study of Elderly [35]		Females	Males
Framingham Heart Study(1988) [36]	Males Females		
Baltimore Longitudinal Study of Aging [13]	Males		
Gothenburg Prospective Study [4]	Males Females		
Framingham Heart Study (1991) [2]	Males Females		
Harvard Alumni (1986) [37]	Males		
Honolulu Heart Program [38]	Males		
Glostrup (Denmark) Longitudinal Study [39]		Males Females	
Kaiser Permanente Medical Care Program [40]	Males	Females	
Lipid Research Clinics Program (in some cases)[41]	Males	Females	

Five Newer Studies of Weight Loss and Mortality: Additional information about the effects of weight loss on mortality is found in five recent analyses of weight loss and subsequent mortality, four of which report increased mortality associated with weight loss. Each of the studies focuses on a different population group. Lee and Paffenbarger[17] found increased mortality with weight loss among 11,703 male Harvard alumni. Pamuk et al.[15] found increased mortality with weight loss in a cohort of 2,453 men and 2,739 women, age 45 to 74 years old at the time of their first examination in the National Health and Nutrition Examination Survey. Blair et al.[1] found increased mortality with weight

loss in 10,529 middle aged males at risk of heart disease in the Multiple Risk Factor Intervention Trial. Higgins et al.[42] found increased mortality with weight loss among 2,500 middle-aged participants in the Framingham study. In contrast, Williamson et al.[43] found decreased mortality with voluntary weight loss among 43,457 overweight, never-smoking US white women in the Cancer Prevention Study.

Each of the studies controls for important factors which could cloud interpretation of the results of the study, including pre-existing illness, smoking, age and baseline weight. Three of the studies control for physical activity.

It is generally assumed that weight loss is essential for maximizing life expectancy for overweight individuals, but this assumption was not borne out in the recent studies, where, in only one instance was weight loss found to improve risk of mortality for heavier subjects. Specifically, only overweight women with obesity-related conditions who voluntarily lost weight saw a decreased risk of mortality in the Cancer Prevention Study;[43] women who intentionally lost weight who were free of pre-existing illness did not see a clear improvement in life expectancy. In none of the other four studies was weight loss associated with improvements in life expectancy, regardless of initial weight. On the other hand, the most overweight individuals did not experience the negative impact of weight loss to the same degree as those who were at lower BMI initially in the NHANES[15] and the MRFIT[1] populations, where excess mortality was significantly associated with weight loss only in the moderately overweight and lowest-weight individuals (BMI below 26 in NHANES and below 28.82 in the MRFIT data).

A very important limitation to all of the studies considered in the two critical reviews summarized above, as well as in three of the newer studies, is lack of control for an absolutely critical variable – lifetime weight pattern. These analyses are based on weights measured at only two points in time. There is no reason to assume that a weight loss or gain between two time points is representative of a lifetime trend in weight. This is well–demonstrated in the Harvard alumni analysis, where Lee and Paffenbarger had access to information about lifetime weight changes for a subset of 7,818 of the 11,708 subjects, and were able to calculate a measure of weight variability – mean lifetime weight loss. They found that the subjects who either gained or lost the most weight during the study period had also experienced the most weight fluctuation over their lifetimes. They suggested that total weight loss and weight gain could be markers for weight cycling, and that weight cycling, rather than weight loss or gain, may have been the factor actually associated with increased mortality.

Only two of the five newer studies discussed here (MRFIT[1] and Framingham[42]) made use of several weights over a number of years so that it is certain that the weight loss documented during the observation period was not, in actuality, a reflection of weight cycling. In both of these studies, weight loss was associated with increased mortality.

The other glaring limitation of all but one of the above–discussed studies of weight loss and mortality is lack of information about whether the weight losses reported by subjects were due to voluntary weight loss efforts or due to

illnesses causing weight loss. Most of the researchers who looked at mortality and weight change made heroic efforts to control for the presence of disease conditions which could cause weight loss, but in only one study[43] were subjects actually asked whether their weight changes had been intentional. Firm conclusions about weight loss and mortality cannot be drawn when information about volition of weight loss has been omitted from so many studies.

As serious a flaw as this omission is, it may not be a fatal flaw. Even if the volition of the weight change were known, the picture could still be cloudy. Whereas it is assumed that involuntary loss would be more closely associated with mortality, voluntary weight loss does not necessarily imply that healthy lifestyle was enhanced. For example, voluntary weight loss could be achieved by health-threatening unsafe diet practices,[44] initiation of smoking for the purpose of reducing weight, use of recreational drugs or in response to learning of a diagnosis of a weight-related illness.

In support of the idea that volition of weight loss does not invalidate these studies, it should be noted that volition of weight loss has been assessed in four major weight change studies. In a population of older Iowa women, French et al.[45] found that, whether weight loss in early life had been intentional, unintentional, or both, women with more weight variability had higher disease prevalence than stable-weight women. In the Cancer Prevention Study cohort, Hammond and Garfinkle[30] found that weight loss had a similar association with mortality, regardless of intention. In a later analysis of weight and mortality data in the same Cancer Prevention Study cohort, Williamson et al.[43] found that the

association between intentional weight loss and longevity in middle-aged overweight women depended on health status. Intentional weight loss among women with obesity-related conditions was generally associated with decreased premature mortality, whereas among women with no pre-existing illness, the association was equivocal.

Based on this finding, Williamson et al. [43] suggested that other studies which eliminated subjects with such illnesses from analysis may have inadvertently removed those persons for whom weight loss may been most beneficial. This places researchers who do not know whether weight loss was intentional in a double bind, because the principle means available for eliminating the effects of illness on weight is to identify individuals with health conditions and either eliminate them from analysis or control for the conditions in data analysis.

Summary - Studies of Weight, Weight Loss and Mortality: No matter how carefully one scrutinizes the available body of published research on weight, weight loss and mortality, definitive conclusions about the effectiveness of weight loss in increasing longevity cannot be drawn. There is evidence that being slim is associated with better life expectancy, but there is definitely not compelling evidence that weight loss will produce a comparable life expectancy as a lifetime of slenderness. The fact that so many of the 23 studies of weight loss and mortality considered here suggest negative consequences of weight loss justifies questioning the conventional wisdom that calls for weight loss for the 50% of the population who are "above average" weight.

Weight Gain / Regain and Health

The Effect of Weight Gain on Mortality: Weight gain seems to affect risk of mortality differently depending on the amount gained. In several population-based prospective studies, larger amounts of weight gain were associated with increases in mortality. Specifically, Lee and Paffenbarger found that Harvard alumni experienced increased mortality when BMI increased to greater than 26 in a 1993 study,[46] and also when weight gain over an 11-16 year period exceeded 5 kg (a 1992 study[17]). For Paris Civil Servants,[34] a gain of more than 6.5 BMI units was associated with increased mortality. Among employees of the Western Electric Company,[3] the group which gained an average of 37% had increased mortality compared to employees with stable weight.

Studies of modest weight gain have yielded conflicting results. Willett et al.[47] demonstrated a linear increase in fatal and nonfatal coronary heart disease with net weight gain between ages 18 and ages 33-55 years among women in the Nurses Health Study. Even a weight gain as low as 5 to 11 kg. was associated with a statistically significant increase in heart disease deaths compared to stable weight. Lack of control for physical activity and for weight cycling are limitations of this study. In contradiction to the findings of Willett et al.,[47] when Andres et al.[14] looked closely at 13 major epidemiological studies, they found that the lowest mortality rates were generally associated with modest weight gains. The highest mortality rates occurred in adults who either had lost weight or had gained excessive weight. See Table 2.

Table 2 – Pattern of Weight Change Associated With Lowest Mortality Reported Separately for Males and Females by Andres et al.[14]

Population Studied	Moderate Gain	No Change	Moderate Loss	No Association
Paris Civil Servants[34]	Males			
Dutch Longitudinal Study of Elderly[35]	Females		Males	
Western Electric Company Employees[3]		Males		
Framingham Heart Study(1988)[36]	Males Females			
Harvard Alumni Heart Study (1992)[17]	Males			
Baltimore Longitudinal Study of Aging[13]	Males			
Gothenburg Prospective Study of Men and Women[4]	Males Females			
Framingham Heart Study (1991)[2]	Males Females			
Harvard Alumni (1986)[37]	Males			
Honolulu Heart Program[38]	Males	Males		
Glostrup (Denmark) Longitudinal Study[39]				Males Females
Kaiser Permanente Medical Care Program[40]	Males			
Lipid Research Clinics Program (in some samples)[41]	Males			

The Effect of Weight Regain on CVD Risk Factors: It is universally accepted that weight gain is associated with worsening of health risk measures, although few studies specifically quantify this phenomenon.[10, 48] A clinical question of utmost importance is whether it is better to have lost and regained

than never to have lost at all.

Dearth of Research: Given the facts that the vast majority of individuals who lose weight regain it, and that the rate of weight regain is proportional to the rate of weight loss,[49] there is an incredible dearth of published research on the effects of weight regain on health risk factors.

The surest way to induce weight gain is to induce weight loss. This can be seen by looking closely at data tables from large, randomized controlled clinical trials which have demonstrated that weight loss is associated with reductions in blood pressure.[50, 51, 52, 53, 54] In all cases, the intervention groups, on average, weighed less at the end of the observation period than the control groups who had not been prescribed weight loss, and had slightly lower blood pressure than controls. However, because the weight losers regained lost weight, the "weight losers" experienced more weight gain over the observation period that did the control groups. For example, in both the Hypertension Control Program[50] and the Hypertension Prevention Trial,[54] the intervention group weighed slightly less than the control group at the end of the five-year trial, but had gained more than twice as much weight as the control group over the five years.

The Difficulty of Interpreting Existing Research: After an individual regains all the weight lost, are his blood lipids, blood pressure, and blood glucose going to be the same, better, or worse than their pre-weight-loss levels? Published literature is not very helpful in answering this question. One of the most serious barriers to answering this question is the common practice of

lumping weight losers with weight regainers when research findings are summarized. Almost all published studies of weight loss and health risk factors include some data on subjects who have regained all of their weight, but the effect of weight regain, *per se*, is obscured because data are reported in terms of **average** weight loss within a cohort at the end of some observation period. Periods of weight loss and regain are not examined separately.

To give one of dozens of examples, Schotte and Stunkard[55] looked at the effects of weight changes on blood pressure in 137 hypertensive and 164 normotensive obese adults. There was an average decrease in blood pressure during the weight loss intervention period and an average increase in blood pressure during the follow-up period. However, the follow-up period was not a time of consistent weight gain. At the time the follow-up measurements were taken, some of the hypertensive subjects were still losing weight, some had regained part of the weight, others had regained all, and others had gained more than they had lost, yet blood pressures for all subjects were averaged together at the times measurements were taken.

Schotte and Stunkard did attempt to separate out the effects of degree of weight regain on blood pressure, by dividing subjects into quartiles according to their "ability to maintain weight loss." One of the quartiles included the individuals who had regained all the lost weight, but included others as well. All quartiles showed increases in blood pressure during follow-up. There was little statistical relationship between the amount of regain and the amount of increase in blood pressure.

A 1991 study by Wing et al.[56] has been widely cited as evidence that weight loss is beneficial, even if weight is regained.[57] Wing and colleagues looked at long-term glycemic control in obese Type II diabetics who underwent weight loss and some subsequent regain. Thirty-six patients were randomly assigned to either a standard behavior therapy (BT) weight loss program, or to a behavior therapy program which included 8 weeks of very low calorie diet (VLCD). One year after the end of treatment, there was no difference between the two groups in weight, because the VLCD group regained more weight than did the BT group. Both groups showed improvements in glycemic control as evidenced by reductions in medication requirements. The VLCD group also maintained several measures of slightly improved glycemic control one year after treatment (fasting blood glucose and glycosylated hemoglobin), despite the fact that these individuals experienced a greater weight gain during the post-treatment period than did the individuals in the BT group, and despite similar exercise patterns, in both groups.

Although this research suggests lingering positive effects on risk factors after some weight regain, results for subjects who regained all the lost weight were not reported. In an earlier study of diabetics by the same research group,[58] improvements in the same risk factors (fasting blood glucose and glycosylated hemoglobin) were noted only in subjects who whose net weight loss at one year follow-up was greater than 5% of body weight. In the 41% of subjects who were not able to sustain that degree of weight loss, glycosylated hemoglobins returned to pre-weight loss levels. In the other 18% of subjects who regained

more weight than they had originally lost, there was an increase in this risk factor to higher than pre-weight loss values.

In a more recent study of 202 overweight individuals, Wing et al.[59] did differentiate individuals who regained all their weight from those who regained only part. CVD risk factors of total cholesterol, HDL, LDL, triglycerides, blood pressure, per cent body fat, and waist to hip ratio were documented at baseline and 30 months after a 6-month weight intervention. Of greatest interest were comparisons in CVD risk factors among 3 subgroups of the population – (1) 25 individuals who had remained weight stable, (2) 28 who had regained all of a moderate weight loss of about 5 kg., and (3) 31 who had regained all of a 12-kg weight loss. These 3 subgroups were very similar with respect to all risk factors at 30 months. The group which had regained 12 kg. had slightly better final values for blood pressure and waist to hip ratio than the group regaining all of the smaller weight loss. The fact that the average values for CVD risk factors over the 30 months of the study were lower for weight regainers than for weight stable individuals led the authors to conclude that weight loss followed by regain could be more beneficial than remaining at a stable high weight. It should be noted that there were very few individuals in each of the 3 subgroups.

Weight Regain and Visceral Fat Stores: One risk factor for cardiovascular disease is visceral fat accumulation. It has been suggested that weight regained after weight loss may be preferentially deposited in visceral fat stores, as opposed to subcutaneous depots, resulting in a net worsening of atherogenic risk. There have been several studies quantifying changes in

visceral fat with weight loss, [60, 61, 62, 63, 64, 65] but only five have been found that describe changes in visceral fat stores or waist–hip ratio with weight gain or regain. Bouchard et al.[66] overfed 12 pairs of identical male twins for 84 days by 1,000 kilocalories per day. Increases in body fat did not correlate with increased visceral fat, although some sets of twins were found to be more prone to store fat in the abdominal visceral area than were other sets. Van der Kooy et al.[67] followed 32 obese subjects who lost and regained 11.9 kg. Weight regain did not result in greater body fatness, and there was no indication of preferential deposition of visceral fat relative to subcutaneous fat. Similarly, Hensrud et al.[68] found that weight regain did not result in increased fat mass or increased waist–hip ratio in 24 obese women who spontaneously regained from 19–216% of lost weight four years after significant weight reduction. Hainer et al.[69] found that waist–hip ratio did not change among women who had regained substantial amounts of weight one year after a very low calorie diet. Wing et al.[59] found that neither per cent body fat nor waist to hip ratio increased among 31 individuals who had lost and regained 12 kg.

None of these five studies support the idea that regained weight is preferentially deposited in visceral fat depots. The possibility cannot be ruled out that such a preferential fat deposition does occur, although the bulk of the animal literature does not support this hypothesis either.[70]

Summary of Weight Regain and Risk Factors: In summary, the important clinical question of whether complete weight regain results in a positive, neutral, or negative effect on cardiovascular risk factors has not been

definitively answered at this time.

Factors Other than Weight and Weight Change Known to Affect Blood Lipid Concentrations and Blood Pressure

Physical Activity / Fitness Level: The extreme importance of physical activity for preventing chronic disease has been well understood only in recent years. As of 1992, the American Heart Association officially recognized physical inactivity as a risk factor for cardiovascular disease, as important as high blood pressure, smoking, weight and high blood cholesterol.[71] Physically inactive people have almost twice the risk of cardiovascular disease as those who engage in regular physical activity.[72]

The powerful protective effect of physical fitness against early mortality was demonstrated by Blair et al.[73] in a population of healthy men and women. Among individuals with high blood pressure, elevated cholesterol, elevated blood sugar, high body mass index or who smoked cigarettes, those who were physically fit had far lower risk of mortality than those who were not fit. Individuals with a family history of death from coronary heart disease who were physically fit were 3–6 times less likely to die of coronary heart disease than individuals with no family history but with low levels of fitness.

Lower mortality rates from cancer of combined sites have been shown for both men and women in higher categories of physical fitness.[74] Physical activity also appears to have other, additional health benefits. Physical activity results in caloric expenditure which in turn enhances weight loss and control, and is

therefore important in the management and prevention of obesity. Physical activity has been associated with the prevention of osteoporosis in postmenopausal women.[75, 76] In addition, regular physical activity can improve glucose tolerance and insulin sensitivity.[77] It has been reported that physical activity can help prevent and treat depression and anxiety.[78] Increased physical activity, independent of dietary changes, can improve blood lipid profiles and blood pressure.[77]

The bulk of the exercise and health research indicates that moderate levels of physical activity exert significantly protective effects, however two recent reports suggest that there is a threshold effect, such that only more vigorous exercise produces health benefits. Paffenbarger et al.[46] and Marrugat et al.[79] found that vigorous physical activity, but not total activity, was protective.

Since physical activity independently affects weight, blood pressure, HDL, and total cholesterol, without documentation of exercise practices, the interpretation of weight and CVD risk factor data is difficult.

Nutritional Factors: There is not universal agreement on the precise relationships between specific nutrient intakes and risks of CVD. It is widely accepted that intakes of total fat, saturated fat, polyunsaturated fat, monounsaturated fat, dietary cholesterol, and caloric balance have effects on blood lipids, [131] however individuals differ substantially in responses to changes in dietary lipids. Factors that predict response to dietary lipids are poorly defined but are likely to be largely genetic.[80] Other dietary factors thought to have effects on either blood lipids or CVD risk include fatty acid structure (*cis*-

versus *trans*-isomers of natural fatty acids), omega-3 fatty acids, soluble fiber, anti-oxidants (including vitamin E, vitamin C, and beta-carotene), magnesium, chromium, copper, zinc, vitamin B_6, nicotinic acid, alcohol, [80] iron [81] and folic acid.[168] Nutrition factors reported to be related to high blood pressure include sodium, alcohol, calcium, potassium, magnesium, chloride and phosphorus. [82, 83, 84]

Genetic Contributions to Abnormal Blood Lipid Patterns: Genetic contributions to CVD can be made by mutations in genes which code for various lipoproteins. Blood lipid concentrations will be affected by alterations in genes which code for any of the proteins which control lipoprotein synthesis, lipoprotein processing, and lipoprotein breakdown.[85] Synthesis proteins include the apolipoproteins (A-I, A-II, A-IV, B, CI, CII, CIII, D, E, and apo(a)). Processing proteins include lipoprotein lipase, hepatic triglyceride lipase, lecithin cholesterol acyltransferase and cholesteryl ester transfer protein. The breakdown proteins include the LDL receptor, chylomicron remnant receptor and the scavenger receptor.

Within-Person Fluctuations of Serum Cholesterol: Cyclical variations are found in many biochemical measurements in both humans and animals.[86, 87] It is not possible to quantify the extent to which these variations are responses to seasonal changes in temperature, exercise, duration of sunlight, diet, or intrinsic biologic rhythms. Biologic variability in total cholesterol has been recognized for decades. Variability has been recognized from day to day, week to week, month to month and across seasons. Hegsted et al.[88] reviewed data from 11

experiments reported in the literature in which repeated cholesterol determinations were made on the same subject. Whether subjects were hospitalized, free living, or in metabolic wards, intra-individual variances were very substantial, ranging from a low of 7 mg/dl in subjects consuming a formula diet, to a high of 48 mg/dl when there was very little dietary control.

Although day to day variability is a consistent finding, some individuals have more variability than others. Mogadam et al.[89] observed variations of more than 20% in the mean serum cholesterol in 75% of 20 male and female subjects age 22 to 63 followed for four weeks. The fluctuations followed no predictable pattern, i.e., they were up and down from week to week at random, and were unrelated to age, gender or the serum concentrations of lipoproteins. Groover et al.[90] studied 177 officers in the Pentagon over 5 years, obtaining at least 6 cholesterol determinations on each individual each year. A variation of less than 20% was observed in 20% of the cohort, while a variation over 50% was observed in another 21%. During the study, all 15 of the myocardial infarctions occurred in the men whose cholesterol concentrations had varied by 55% or more. Bookstein et al.,[91] in a study of 51 male and female volunteers age 19-59, found that the considerable day to day variability in cholesterol concentration was not dependent on the concentration of cholesterol. In other words, individuals with higher mean cholesterol concentrations did not experience more variability than individuals with lower mean cholesterol concentrations.

Seasonal Variations in Blood Cholesterol Levels: Harlap et al.[87] reported that nine studies have shown seasonal variations in blood cholesterol

levels. Six of the studies were based on populations living in relatively cold Scandinavian climates, two on North American populations, and one on residents of Jerusalem, a hot climate. Harlap also notes that three other studies (in Scandinavia, North America and Australia) found no evidence of seasonal variations, but these three studies were based on very small samples. In general, higher levels occur in autumn or winter, with a nadir in late spring and early summer.[87, 92, 93, 94] Gordon et al.[95] carried out a thorough analysis of seasonal variations of plasma lipids in 1,446 hypercholesterolemic men who comprised the placebo group in the Lipid Research Clinics Coronary Primary Prevention Trial. They found highly significant seasonal trends for total cholesterol, LDL, and HDL, which peaked in the first month of winter. There was no correlation between the seasonal cycles and body mass index or seasonal intake of total calories, fat or cholesterol. Total cholesterol and LDL variations were inversely, but significantly correlated with hours of daylight and HDL-cholesterol was positively and significantly associated with ambient temperature. They concluded that there was no doubt that seasonal plasma lipid and lipoprotein cycles exist, although etiologic mechanisms remained uncertain. In a recent review Kritchevsky[96] reported that seasonal variations in plasma lipids have been reported in many animal species, including rats, rhesus monkeys, vervet monkeys, baboons, woodchucks, badgers and hedgehogs. He suggests that the seasonal variability in cholesterol may be related to changes in hormonal levels or in enzyme activity, and points out that not all subjects display the variation, even when under the same environmental conditions.

Rippey[97] has pointed out that seasonal changes in lipids are not large in relation to between-person variation or within-person changes from day to day. Nevertheless, the seasonal differences are as large as those that have been found in many metabolic experiments. Therefore, season is a possible confounding variable when comparing lipid levels over time.

Alcohol Consumption: Many epidemiologic studies have shown that light to moderate alcohol intake is associated with lower mortality from heart disease, when compared to abstention from alcohol. [98, 99] This effect appears to be mediated by an increase in plasma HDL levels associated with increased alcohol consumption. Alcohol intake also increases blood pressure.[100] In the MRFIT population, Suh et al.[101] found a dose-response relationship between the number of drinks per day and risk of CVD.

Medical Conditions and Medications: A number of medical conditions and medications can exert effects on blood lipids, blood pressure or weight. For example, neoplastic disease is well known to decrease cholesterol and in the case of colon cancer it has been argued that it may do so years before its clinical presentation.[102] Fever, dehydration and recent myocardial infarction affect cholesterol concentrations. Illnesses such as minor viral infections may reduce cholesterol in some individuals.[103] Some diseases produce secondary hyperlipidemias, including hypothyroidism, nephrotic syndrome, renal failure and liver disease. Diabetes is associated with elevated blood pressure and cholesterol levels, although it cannot be said to be causative for these

conditions. Any analysis of weight, cholesterol and blood pressure should take into account subjects' medical conditions and medications which could exert independent effects on cholesterol, blood pressure or weight.

Tobacco Use: It is essential to control any data analyses of weight and health risk factors for tobacco use. Cigarette smoking is associated with weight loss,[104, 105] and smoking cessation has been shown to cause weight gain,[106] but stopping smoking is associated with decrease in mortality risk. Smoking has been associated with higher concentrations of serum cholesterol and blood pressure in some (not all) studies, and with higher waist to hip ratio.[107] Smokers have increased mortality risk from heart disease and cancer.[131]

Age: Age influences serum lipids. It is frequently not appreciated that both cholesterol and triglycerides are at their lowest in adolescence in both boys and girls. In men it reaches its maximum by the mid 40's but in women a rapid rise occurs at around the time of the menopause. The increases with age are more marked in people with the higher levels.[92] Blood pressure also tends to increase with age, perhaps in response to declining renal function and increased peripheral resistance with aging.[108]

Mental Health / Stress: The relatively new field of psychoneuroim–munology is producing evidence of what has been known on an intuitive level for centuries – that mental health affects physical health. The brain and the immune system are linked via the autonomic nervous system and neuroendocrine outflow from the pituitary.[109] Support for the concept that mental health affects heart

disease risk is found in the work of Ornish et al.[110] in which regression of coronary artery lesions was observed in patients whose lifestyle changes included one hour per day of stress reduction plus group social support for one year.

Bjorntorp has published a thorough review of visceral obesity[111] in which he suggests that visceral fat deposition may be the result of environmental stress interacting with neuroendocrine aberrations in genetically-predisposed individuals. Neuroendocrine aberrations in individuals with visceral fat deposition include excessive secretion of cortisol in response to environmental stressors and ACTH, depressed growth hormone concentrations and abnormal hemodynamic response to stress mimicking the "defeat reaction" observed in animals faced with overwhelming stress.

The defeat reaction, observed in female primates, has produced the endocrine profile of visceral obesity in the primates. Female cynomolgus monkeys in a defeated, uncontrollable situation over time develop enlarged adrenal glands, decreased sex steroid secretion, insulin resistance, decreased glucose tolerance, hyperlipidemia, hypertension and coronary atherosclerosis, with accumulation of triglycerides in the visceral depots.[112] Male cynomolgus monkeys also develop atherosclerotic traits in response to environmental stress, but in contrast to females, it is the dominant male in socially unstable situations who develops these traits.[113]

Bjorntorp [111] cited epidemiological studies demonstrating that an elevated waist to hip ratio in men is associated with a poor education, physical types of

work, and a low income. Both males and females with elevated waist to hip ratio use medical facilities more frequently, with frequent incidences of ulcers, gastric bleeding, depression and anxiety. He suggested that subjects in difficult socioeconomic situation who have inadequate coping mechanisms may develop the metabolic characteristics associated with heart disease.

Foreyt et al.[114] found that weight cyclers had lower general well-being, less eating self-efficacy, and higher stress than individual of stable weight. It has been suggested that some of the excess mortality observed in weight cyclers could be the result of diminution of feelings of self-worth and increased feelings of helplessness resulting from lack of success in weight loss in the American culture which glorifies thinness.

Weight Cycling and Health

In recent years, concern has been raised about potential negative health effects from weight cycling, generally defined as loss and regain of some amount of weight. Brownell et al.[115] showed that rats who lost weight and then regained it experienced a slow-down in basal metabolic rate, and experienced increases in per cent body fat compared to littermates who were not subjected to weight loss and regain. In a recent thorough review of the animal literature on weight cycling, Reed and Hill[70] concluded that "the published animal literature does not justify any warnings about the hazards of weight cycling."

The human literature on weight cycling, summarized in Table 3 and reviewed below, consists of large-scale epidemiological studies of nine population groups and clinical studies on two small populations. Taken

together, this literature suggests an association between weight variability and cardiovascular disease. In eight of these groups, weight variability was found to be positively associated with either increased CVD[1, 2, 4] increased CVD mortality[1, 2, 3, 116] or increase in some CVD risk factors.[4, 13, 117] In the other three populations, no statistical association was found between weight variability and CVD.[59, 118, 119]

Weight Cycling, Mortality and Cardiovascular Disease: The thrust of most epidemiological studies of weight cycling has been a search for associations of weight variability with mortality and CVD. All-cause mortality was associated with weight variability in six populations - MRFIT,[1] Framingham,[2] Gothenburg males, Gothenburg females,[4] Zutphen males,[119] and Japanese American men,[116] - but not Baltimore males[13] or Charleston residents.[118] Increased CVD or CVD mortality with weight variability was found among five populations - MRFIT,[1] Framingham,[2] Western Electric Company employees,[3] Gothenburg males,[4] and Japanese American men[116] - but not in the Baltimore men,[13] Zutphen males,[119] or Gothenburg females.[4] Table 3 summarizes and compares the available studies of human weight cycling.

Weight Cycling and CVD Risk Factors: Since evidence has been found that weight cycling may be associated with increased deaths from heart disease, several researchers have looked for associations among measures of weight cycling and recognized risk factors for CVD. In a well-designed study, Lissner et al.[13] used data for 846 healthy males age 17 to101 participating in the Baltimore Longitudinal Study on Aging. Three to 16 weights per subject over a 2- to 27-

year time span were used. To define weight variability, weight was regressed on time for each individual, and the standard error of the estimate (SEE) was used as the measure of weight variability. Weight variability was not associated with changes in serum cholesterol, systolic blood pressure, triglycerides or waist to hip ratio, but was associated with a measure of central fat distribution, the ratio of subscapular to triceps skinfolds, and was also associated with decreased glucose tolerance. Increased incidence of diabetes mellitus was also found in weight cycling Gothenburg females[4] but not in Gothenburg males.[4]

One clinical study by Wing et al.[59] identified 59 overweight individuals who experienced 1 weight cycle of either 5 or 12 kg. during a 6–month weight loss intervention and regained all the weight in 30 months. There were no detrimental effects from weight cycling detectable for total cholesterol, HDL, LDL, triglycerides, blood pressure, per cent body fat or waist to hip ratio. In contrast, a positive association was found between weight variability and waist to hip ratio in 87 Connecticut women.[117]

Limitations of Published Studies of Weight Cycling

None of the large epidemiological studies supplying data used for analyses of weight cycling and health outcomes was designed to study weight cycling. Each has limitations which preclude establishment of a causal relationship between weight variability and the endpoints considered. The limitations of these studies are discussed below.

Limitation: Paucity of Weight Data: A severe limitation of most published studies, to date, is that there were too few weights available for each

subject, and the intervals between weights were too long to detect the presence of weight cycles. The study making use of the most weight data was that based on the Framingham data,[2] with 8 measurements over 16 years. Although a great deal of information was available, the two-year interval between weights allows the possibility of extreme weight fluctuation between measurements, which could be completely missed in the data analysis. For the Western Electric Company employees[3] five recalled weights at 5-year intervals were used, which would not allow documentation of more than one weight cycle.

For the Connecticut women Rodin et al.[117] calculated a weight cycling score based on recalled weights over 5-25 years. This complete documentation of life weights was a positive aspect of the study, but the absence of measured weight in both the Connecticut women and Western Electric employees erodes the validity of the measure of weight cycling. Estimates of the validity of recalled weights varies from 0.80 to 0.935 [38, 118, 120] for each measurement. The validity of multiple recalled weights would be much lower than the validity of one recalled weight. In the other weight cycling studies, very few measurements were available. For the Baltimore Longitudinal Study on Aging[13] population, four weight measurements were used for the analysis of weight cycling and mortality. Analyses of the Gothenburg male data[4] and the Honolulu Heart Study data [116] were based on only three measured weights. Analyses of the Charleston Heart Study[119] data and Gothenburg female[4] data were each based on only two measured weights and one recalled weight.

One analysis made use of more measurements, but did not have

comparable amounts of data for each subject. Analysis of the Zutphen Study[119] population included an average of 10.3 measurements over 10 years, with a minimum of four measurements.

Limitation: Inadequate Mathematical Definition of Weight Cycling: The measure of weight cycling used most commonly is the coefficient of variability (CV), defined as the standard deviation of weights divided by the mean weight. The standard deviation and CV are inadequate for studies of weight cycling because individuals who consistently gain or lose weight may have a high standard deviation of weight and CV even if no weight cycling occurred at all. [121]

Only three of the published analyses used measures of weight cycling which separate the linear trend in weight change from the variability around the trend. Each of these based the definition of weight cycling on linear regression of weights on time. In the Zutphen population analysis,[119] weight cycling was quantified as the residuals of the regression. In the Baltimore [13] and the Honolulu Heart Study[116] population analyses, weight cycling was documented as the SEE. The SEE and residuals do separate out the variability due to fluctuations in weight from variability attributable to a consistent trend of weight loss or gain. Neither of these two measures, however, indicate how many episodes of weight loss and regain occurred.

Limitation: Failure to Specify the Number or Size of Weight Cycles: To determine whether weight cycling has an effect on health outcomes, it would be desirable to know how many times weight was lost and regained, and the

magnitude of the weight cycle. No published studies of weight cycling include this information. Only two population studies (Western Electric[3] and MRFIT[1]) actually documented that at least one weight cycle had occurred in the individuals considered to be weight cyclers. Neither of these two analyses documented whether more than one cycle had occurred.

Limitation: Inadequate Information about Potentially Confounding Variables: Many factors affect both weight and CVD risk, including age, physical activity, tobacco use, existence of other health conditions, intake of dietary factors, use of drugs that can affect risk factors, alcohol use and mental health status. None of the previous analyses included all of these factors, and when any of the factors were included, they were often not specified completely enough to adequately control for their potential influences on the outcome measures.

- **Physical Activity**: Physical activity has seldom been documented in studies of weight and mortality. Without documentation of exercise practices, the interpretation of weight and mortality data is difficult because physical activity independently affects weight, blood pressure, cholesterol, insulin resistance and cardiovascular mortality risk.[71] In the weight cycling literature, physical activity has been considered in analysis only in Model C of the Framingham population analysis[2] and in the mortality analysis of the MRFIT data.[1] For the Framingham analysis, physical activity was documented at only one time in the trial. A person's level of physical activity at one point in time is

not likely to be representative of his activity level over 16 years. In the MRFIT analysis by Blair et al.,[1] the measure of physical activity used was not representative of usual physical activity, but rather was the subject's self-assessment of his activity level compared to his peers at the time of entry into the study. This was inadequate documentation to eliminate the confounding effects of exercise on mortality risk because, in the MRFIT population, one of the interventions in the Special Intervention (SI) group was behavior modification to increase exercise. It can be assumed that exercise habits changed after entry into the study.

- **Cigarette smoking:** Smoking can affect weight, blood lipids, and blood pressure. If smoking behavior is not controlled for in data analyses, the conclusions drawn are less certain. In published weight cycling studies, smoking was controlled for in Model C of the Framingham analysis,[2] the Western Electric analysis,[3] the Gothenburg analyses,[4] the Honolulu Heart Study analysis[116] and the MRFIT analysis.[1] However, specification of smoking behavior was incomplete. For example, in both the Framingham and the MRFIT analyses, smoking status was controlled for by including in the regression model the number of cigarettes smoked per day measured once, early in the study. If a person subsequently quit smoking or increased the level of smoking, that was not taken into account, and could have affected the outcome variable in those analysis, mortality.

- **Causes of Weight Change / Volition of Weight Loss**: The most frequently-mentioned criticism of weight change studies is that they do not

differentiate voluntary from involuntary weight loss. As discussed earlier, this may not be a fatal flaw. Only one of the population studies of weight cycling had any indication of intentionality of weight change. Women in the Gothenburg Study [4] were asked whether they had been on weight reduction diets. Being on a weight reduction diet was not associated with increased mortality, even though weight cycling was associated with increased mortality in this study.

In studies of weight cycling and mortality, efforts have been made to eliminate people whose weight variability was involuntary (due to pre-existing illness) in several ways. Most commonly, subjects who died or became ill in the time period immediately after the final weight measurement were eliminated from the analysis, so that weight losses near the end of the observation period due to illness would not be a factor in the analysis. This is a very reasonable method of controlling for pre-existing illness. The length of the lag period between final measurement and the beginning of the observation period for deaths in the studies reviewed here varied from none (Western Electric, Baltimore, and Zutphen studies [3, 13,119]), to shorter than one year (Gothenburg and MRFIT studies[4, 1]), to 5 or 6 years in the Honolulu Heart Study[116] and Framingham study.[2]

The other way researchers have attempted to eliminate the effects of illness on weight is to identify individuals with health conditions and either eliminate them from analysis or control for the conditions in data analysis. When Lissner et al.[4] dropped from analysis Gothenburg women with pre-existing illness, the apparently detrimental effects of weight cycling and weight loss were

no longer noted. Similarly, Iribarren et al.[116] found that weight loss and weight cycling were associated with reduced life expectancy only in men with pre-existing health conditions. Volition of weight loss was not directly evaluated by Iribarren, however all deaths occurring in the five years after the final weight measurement was taken were excluded from analysis, thus eliminating most of the effects of weight loss due to illness. None of the other epidemiological studies of weight cycling eliminated individuals with pre-existing weight-related conditions.

- **Dietary factors:** Of all the published studies of weight cycling or weight change, only the Western Electric Study analysis [3] included control for dietary intake of any nutrient. This would not be considered a serious flaw in studies which used mortality as an endpoint. However, when blood pressure and cholesterol are endpoints of interest, such as in the Baltimore Longitudinal Study on Aging analysis[13] or the study by Wing et al., [59] inclusion of dietary information would be critical.

- **Alcohol use:** Only two studies of weight cycling have taken alcohol consumption into account (Western Electric[3] and MRFIT[1]). In the MRFIT analysis by Blair et al.,[1] the number of alcoholic drinks per week included in the analysis was based on drinking only at baseline. This is less than optimal control for the effects of alcohol, because subsequent increases or decreases in drinking were not taken into account.

- **Mental health status:** None of the studies of weight cycling include

any variables reflective of mental health status.

Summary, Studies of Weight Cycling: The research available suggests that weight loss with subsequent regain may increase risk of heart disease. However, serious methodological limitations in all published studies render the proposed link between weight cycling and negative health outcomes somewhat tenuous.

Table 3 - Selected Characteristics of Published Weight Cycling Studies

Study Population	Subjects	Weight Data Used	Definition of Weight Cycling	Confounding Variables Controlled	↑ in All-Cause Mortality	↑ in CVD Mortality or Heart Disease	Risk Factors Made Worse
Framingham[2] Model A	Residents, Framing-ham, MA. male and female, age 30-62, n=5124	Measured weights at 2-year intervals + recalled weight at age 25	Standard Deviation of 9 BMI's + Mean BMI	Age	Yes	Mortality: Yes Heart Disease: Yes	Not studied
Model B	Same	Same	Same	Age, mean BMI, linear trend of weight over time	Yes	Mortality: Yes Heart Disease: Males: Yes Females: No	Not studied
Model C	Same	Same	Same	Age, mean BMI, linear trend of wt. over time, cigarette/day, physical activity, serum cholesterol, blood pressure, glucose tolerance	Yes	Mortality: Yes Heart Disease: Men: Yes Women: No	Not studied
Honolulu Heart Study [116]	Japanese American men, age 45-68. n=6,537	Three measured weights, approx. 3 yrs. apart	Standard error of the estimate for regression of 3 weights on time	Pre-existing illness, smoking, BMI	Yes, for those w/ existing disease and smokers. No, for healthy never-smokers.	Mortality: Yes for men with existing disease and smokers. No for healthy never-smokers. Heart Disease: not studied.	Not studied

Table 3 (cont'd)

Study Population	Subjects	Weight Data Used	Definition of Weight Cycling	Confounding Variables Controlled	↑ in All-Cause Mortality	↑ in CVD Mortality or Heart Disease	Risk Factors Made Worse
Baltimore Longitudinal Study on Aging[13]	Healthy, well-educated males, age 17-101 during study n=846	For mortality : four measured weights at first four exams of the study. For risk factors: 3-16 weights	Standard Error of the Estimate for Regression of Weights on Time	Age, mean BMI, rate of weight change, pre-existing Illnesses	No	Mortality: not studied. Heart Disease: No	Yes: Glucose tolerance, subscapular: triceps No: Blood pressure, cholesterol, waist:hip ratio
Charleston Heart Study[118]	Random sample, residents of Charleston 291 white males, 300 white fe-males, 153 black males, 184 black fe-males, age 35-70 in 1960	Weight measured in 1960 and 1963 plus recalled weight at age 25	Standard Deviation of 3 BMI's + Mean BMI	Age, mean BMI, change in BMI	No	Mortality: not studied. Heart Disease: not studied	Not studied

Table 3 (cont'd)

Study Population	Subjects	Weight Data Used	Definition of Weight Cycling	Confounding Variables Controlled	↑ in All-Cause Mortality	↑ in CVD Mortality or Heart Disease	Risk Factors Made Worse
Western Electric Company[3]	White male employees, age 40-56 n=2,107	Recalled weights at ages 20, 25, 30, 35, 40	Gain and loss of ≥10% during two five-year periods (n=98).	Age, blood pressure, cigarettes/day, alcohol intake, serum cholesterol, mean BMI	No	Mortality: Yes Heart Disease: not studied	Not studied
MRFIT[1]	Men at high risk for heart disease, age 35-74 at baseline. n=10,529	Weight measured every 4 months for the Inter-vention group and every year for the control group.	2 Measures used: Standard Deviation of 6-21 weights and Loss and regain of at least 5 % of body weight at least one time.	Baseline BMI, smoking, Illness during the study period, blood pressure, use of diuretics, serum cholesterol, alcohol intake , age, race, Initial level of physical activity	Yes, BMI <26	Mortality: Yes, if BMI <26 Heart Disease: not studied.	Not studied
Gothenburg Males[4]	Men born in Gothen-burg, Sweden, in 1913 n=698	Weights measured at ages 50, 54, and 60	Standard Deviation of 3 BMI's + Mean BMI	Mean BMI, net weight change, cigarette smoking	Yes	Mortality: not studied. Heart Disease: yes, but no increase in strokes	No: Diabetes

Table 3 (cont'd)

Study Population	Subjects	Weight Data Used	Definition of Weight Cycling	Confounding Variables Controlled	↑ in All-Cause Mortality	↑ in CVD Mortality or Heart Disease	Risk Factors Made Worse
Gothenburg Females[4]	Random sample of women born in Gothen-burg, in 1908, 1914, 1918, 1922, 1930 age 38, 46, 50, 54, 60 n=1268	Measured weights in 1968-69 and 1974-74 Recalled weight 5 years before first exam.	Standard Deviation of 3 BMI's/ Mean BMI	Mean BMI Net weight change Cigarette smoking Age group	Yes when no control for pre-existing illness; No if pre-existing illness controlled.	Mortality: Not studied Heart Disease: No	Yes: Diabetes
Zutphen[119]	Men in Zutphen, Netherlands, age 40-60 n=630	At least 4 measured weights, mean of 10 weights	Residuals of regression of weight on time	Age Smoking Mean BMI over 10 years Linear trend in weight	Yes	Mortality: Not reported Heart Disease: No (myocardial infarction only)	Not studied

Table 3 (cont'd)

Study Population	Subjects	Weight Data Used	Definition of Weight Cycling	Confounding Variables Controlled	↑ in All-Cause Mortality	↑ in CVD Mortality or Heart Disease	Risk Factors Made Worse
Connecticut Women[117]	Women from New Haven, Connecticut responding to recruitment effort, normal wt., age 21-40 n=87	Recalled weights over lifetime	1. Score on weight history instrument 2. Loss of 10 lbs. or more at least one time 3. Self-designation as "yo-yo dieter"	Age Parity BMI	Not studied	Mortality: not studied Heart Disease: not studied	Yes: waist:hip ratio
Overweights (Wing et al.)[59]	Healthy, non-smoking overweight recruits from Pittsburgh and Minneapolis, male and female, age 25-45, n=202	Measured weights at 6-month intervals	Loss and complete regain of either 7 or 12 kg. (n=59)	Baseline values of each risk factor.	Not studied	Mortality: not studied. Heart Disease: not studied.	No: Total cholesterol, HDL, LDL, triglycerides, blood pressure

Blood Lipids and Blood Pressure as Risk Factors for CVD

Total Cholesterol: Although information on blood lipid subfractions allows more accurate calculation of CVD risk, total cholesterol concentrations are still valuable in defining level of risk for CVD. There is a large body of epidemiologic evidence supporting a direct relationship between the level of total cholesterol and rates of CVD.[122, 123, 124] For both males and females, cohort studies show an association between total blood cholesterol levels and a CVD rate. This association is continuous throughout the whole range of cholesterol levels in the population and is particularly strong at the higher levels of serum cholesterol. Clinical and epidemiological studies show that a reduction in total serum cholesterol of 1% is associated with a 2-3% reduction in CVD rates.[125] The 1993 National Cholesterol Education Program recommendations [131] promote measurement of total cholesterol as the primary screening for CVD risk: "In individuals free of CVD, total cholesterol levels less than 200 mg/dl are classified as desirable blood cholesterol, those from 200-239 mg/dl as borderline-high blood cholesterol, and those 240 mg/dl or greater as high blood cholesterol."

Although low density lipoprotein-cholesterol (LDL) is a more sensitive indicator of risk, most cholesterol in serum is contained in LDL, so the concentration of total cholesterol in most people is highly correlated with the concentration of LDL.

HDL Cholesterol: High Density Lipoproteins (HDL) normally carry 20-

30% of total cholesterol. HDL concentrations are inversely correlated with CVD rates over a broad range of HDL levels. For every 1-mg/dl decrease in HDL, the risk for CVD is increased by 2-3 per cent.[126] Low HDL (<35 mg/dl) is classified as a major risk factor for CVD, and high HDL (60 mg/dl and above) is considered a negative risk factor.[131] In elderly Dutch men, HDL was most strongly associated with the risk of a first coronary event. [127]

A variety of factors contribute to low HDL concentrations. Genetic influences are known. [128, 85] Inherited influences are accentuated by lifestyle, including cigarette smoking and physical inactivity and excessive caloric intake leading to obesity. Certain drugs, including beta-adrenergic blocking agents (beta blockers), anabolic steroids and progestational agents, also reduce HDL. Smoking cessation, increasing physical activity, and weight reduction in overweight individuals can increase HDL concentrations. Most lipid-lowering drugs have the potential to raise HDL concentrations. No clinical trials have been reported which specifically test the efficacy of raising HDL in prevention of CVD.[131]

The Ratio of Total Cholesterol to HDL: The ratio of total cholesterol to HDL has been identified as the most accurate predictor of coronary heart disease at all ages in the Framingham population[129] and in the elderly males of the Zutphen population.[127] In the Physicians Health Study cohort, the ratio of total cholesterol to HDL was a significant predictor of risk for myocardial infarction; after adjusting for other risk factors, a change of one unit in the ratio of total cholesterol to HDL was associated with a 53% reduction in risk.[130]

Low Density Lipoproteins: LDL typically contain 60-70% of total serum cholesterol. LDL is a sensitive measure of CVD risk. LDL is the primary target of cholesterol-lowering therapy because direct clinical trial evidence for the benefit of lowering LDL is strong. In young men and premenopausal women, LDL concentrations below 160 mg/dl are considered optimal, 160 to 220 mg/dl are considered moderately high, and 220 mg/dl is considered very high.[131]

Triglycerides: Serum triglycerides concentrations are positively correlated with CVD in most epidemiologic studies, but when risk calculations take into account total cholesterol and HDL, triglyceride levels are often no longer statistically significant predictors of CVD.[131, 132]

Hypercholesterolemia as a Risk Factor for Mortality from Non-CVD Causes: It should be noted that the relationship between serum cholesterol and all-cause mortality is far different than that between serum cholesterol and the risk for coronary heart disease. Allred[133] described the relationship between serum cholesterol and all-cause mortality as a U-shaped curve in males, where low cholesterol concentrations were associated with an equally high risk of all-cause mortality as elevated concentrations. In the middle range of cholesterol concentrations (representing about 70% of men), there was no association between cholesterol concentration and mortality. In women, Allred found no change in risk of all-cause mortality as serum cholesterol concentrations increased above 160 mg/dl. It is known that cancer risk, especially lung cancer, is elevated in both males and females when serum cholesterol concentration is

less than 160 mg/dl.[134] There is lack of consensus on whether early-stage cancers cause a lowering of blood cholesterol levels. The risk of hemorrhagic stroke in males has been shown to decrease as serum cholesterol increases.[135]

Blood Pressure as a Measure of CVD Risk: Nonfatal and fatal cardiovascular disease - including coronary heart disease and stroke - as well as renal disease, and all-cause mortality, increase progressively with higher levels of both systolic and diastolic blood pressure.[136] These relationships are strong, continuous, graded, consistent, independent, predictive, and etiologically significant. In the general population, risks are lower for adults with an average systolic blood pressure of 120 mm Hg and an average diastolic blood pressure of less than 80 mm Hg. Higher levels of either systolic or diastolic blood pressure, or both together are associated with increased risks of morbidity, disability, and mortality. For blood pressure, meta-analyses of studies of drug treatment for hypertension show that a reduction of 5-6 mm Hg in mean diastolic blood pressure was associated with reductions in total mortality of 8-42%.[137, 138]

DESCRIPTION OF THE MRFIT DATA BASE

Purpose of the MRFIT

MRFIT was a national, publicly-funded research study extending from 1974 to 1982. Its original objective, as stated in the initial request for proposals, was "to determine whether or not a preventive program directed at the reduction of serum lipids, reduction of blood pressure and reduction or elimination of cigarette smoking among men aged 40-59 who are at high risk of coronary heart disease from a combination of these risk factors can result in a significant reduction in the incidence of myocardial infarction and death from coronary disease over a six year primary intervention clinical trial."[139] In 1972-73, funds to conduct the study were awarded to 22 clinical centers, a coordinating center, a central laboratory, standardization laboratory, ECG centers and a drug distribution center.

Subjects

To be selected for the study, men had to be between ages 35-57, at the upper end of the risk spectrum for heart disease because of elevated cholesterol, elevated blood pressure, or smoking, but could not have any evidence of the existence of heart disease. After screening over 370,000 men, 12,866 meeting the inclusion criteria were randomly assigned to either the

Special Intervention (SI) group or the Usual Care (UC) group. Excluded from the study were men who seemed unsuitable for long-term dietary intervention, including those with blood cholesterol higher than 350 mg/dl, those taking medication for diabetes and those following prescribed diets incompatible with the MRFIT dietary protocol. Excessive alcohol intake and gross obesity were also grounds for exclusion. Because of the heavy demands of time and cooperation required of MRFIT participants, random sampling was not possible. A convenience sample was used, where men were solicited via advertisements for free health screening. Because there was not a probability sample and because subjects were atypical in that they were at high risk for heart disease, the results of the MRFIT study could not be generalized to the entire adult male population.

Data Collection

All 12,866 participants underwent an extensive three-phase screening, during which baseline health and dietary information was documented. Subsequently, all participants were invited back for extensive annual medical exams. Additional data were collected on members of the SI group every four months, including documentation of weight, blood pressure, cholesterol, and smoking status.

Nutrition Data Collection: The primary method used to document nutrient intake in the MRFIT was the 24-hour dietary recall. This method was considered adequate for the research protocol of MRFIT because the unit of analysis was the mean intake for the entire SI or UC group of each nutrient of

interest. Twenty-four-hour dietary recalls were collected at baseline and at years 1,2,3, 5, and 6 for both SI and UC group members.

Food intake data from 24-hour dietary recalls was converted to nutrient data in a computerized process, developed collaboratively by MRFIT staff and staff of the Lipid Research Clinic, with oversight by the National Heart, Lung, and Blood Institute (NHLBI) and input from the United States Department of Agriculture. The nutrient data base initially set up in 1973, called the NHLBI Table of Food Composition, used *Agricultural Handbook No. 8*[140] as the major reference, with updated figures for fatty acids and dietary cholesterol found in the scientific literature and from food manufacturers. When *Agricultural Handbook 456*[141] became available in 1975-76, data were compared and, where appropriate, updated.

Once the data base was established, NHLBI established the Nutrition Coding Center (NCC) in the Department of Biometry, School of Public Health, University of Minnesota. The NCC was responsible for maintaining and updating the data base, coding dietary records collected in both the Lipid Research Center Study and the MRFIT, and training field nutritionists in data collection procedures. Nutrient information for margarines, shortenings, and other processed foods was obtained from food manufacturers and was routinely updated in the data base.[142]

The data base was most complete with respect to dietary fats, because it was developed specifically for heart disease research which focused on modification of total fat, cholesterol, saturated fat and polyunsaturated fat. Data

on other nutrients, such as water-soluble fiber and folic acid were most likely not as reliable as the dietary fat data, because not all foods had been analyzed for these nutrients at that time, and because laboratory methods for detecting several nutrients have been refined considerably since that time.

Physical Activity Data: To document physical activity among MRFIT participants, the Minnesota questionnaire to assess leisure time physical activity (LTPA) was administered to all participants at baseline, and at annual visits 1, 4, and 6. This questionnaire lists 18 major activity groups and 62 individual physical activities. Subjects indicated the number of occasions per month during the previous 12 months that they performed each activity, and its average duration in minutes. Trained interviewers helped with the process at all but baseline assessment. Activities included in the questionnaire were classified as light (requiring 8.4 to 16.8 kJ/min.), moderate (requiring 18.9 to 23.0 kJ/min.), or heavy (25.2 kJ/min. or more). The instrument had been previously validated against treadmill exercise performance and energy intake from dietary records,[143, 144] and has subsequently been found to predict mortality in the MRFIT population.[145]

Another measure of habitual physical activity pattern available in the data set was the participant's opinion of his own physical activity compared to others his age (much less active, somewhat less active, about the same, somewhat more active or much more active). Although this is a subjective measure, it has predicted mortality in the MRFIT population, has been used as a covariate in several analysis of the MRFIT data by the MRFIT Research Group [1, 146] and has

been found to correlate with risk factors in ways physical activity levels would be expected to do. Exercise opinion was asked at each annual visit.

The study protocol for MRFIT included a measure of physical fitness - a submaximal graded treadmill exercise test, with stepwise increase of slope and speed until a predetermined target heart rate was reached or until the test was terminated for other reasons such as heart rhythm irregularities or subject discomfort. Target heart rates were based on age, and were estimated to represent 85% of the predicted maximal heart rate.[147] Such a test is an established procedure for evaluation of suspected coronary heart disease and for assessment of cardiopulmonary fitness. The number of minutes a subject is able to continue the test ("exercise duration") is considered an accurate measure of physical fitness.[148] Graded exercise tests were performed as part of the electrocardiogram at annual visits.

Tobacco Data: Use of tobacco by MRFIT subjects was extensively documented. For the SI group, the average number of cigarettes per day over the preceding four months is recorded at each visit, every four months, over the entire study period. For the UC group, average number of cigarettes over the past four months is recorded annually. In addition to self-reported tobacco use, blood levels of the compound thiocyanate were measured on each subject to independently verify the subject's self-report on smoking status. Thiocyanate levels are elevated from cyanide in tobacco smoke. They can also be raised by consumption of certain foods (the Brassica genus - cabbage, cauliflower, kale, kohlrabi, broccoli, brussels sprouts, turnips, and rutabagas, and also fruit pits

and almonds), and by use of diuretics. Inasmuch as the dose-response curve of number of cigarettes to blood levels of thiocyanate was non-linear, serum thiocyanate levels were used only to verify smoking cessation, rather than to verify the reported dose of tobacco.[149]

Data on Medical Conditions and Medications: For all MRFIT subjects, extensive physical exams and health histories were performed once each year. The presence or absence of 55 different conditions was noted by MRFIT physicians for each subject. Each annual physical exam included a history of medication use over the previous year. Documentation of medication use was very specific for antihypertensive drugs, but most other drugs were identified only by broad category. The categories of medications documented in the data set are as follows:

> Digitalis; nitrates including nitroglycerine; propranolol; lipid-lowering drugs including clofibrate, cholestyramine, sterol-binding resins, beta-sitosterol (Cytellin), nicotinic acid derivatives, neomycin, dextrothyroxine (Choloxin), probucol, estrogens, progestins, heparin, halofinate; drugs for gout including probenicid, allopurinol, or colchicine; insulin or oral hypoglycemic agents; anticoagulants; antibiotics or anti-infection agents; steroids; amphetamines or other stimulants; barbiturates or other sedatives; anti-anxiety drugs including Librium and valium; potassium supplements.

Mental Health Data: Mental health data were collected on 12,772 of the MRFIT subjects, to test the hypothesis that men with a Type A Behavior Pattern would have a higher incidence of first major coronary events. [150] Type A Behavior Pattern was defined to include competitiveness, excessive drive and enhanced sense of time urgency. Behavior patterns were documented in two ways. A validated structured interview was administered to a subset of 3,110

men by highly-trained technicians and psychologists. All subjects took the Jenkins Activity Survey, a 54-item self-administered questionnaire.

Blood Lipid Fractions in MRFIT: The MRFIT study used the most sophisticated criteria for screening for CVD risk available at that time. The blood lipid fractions recorded throughout the study were total serum cholesterol and triglycerides. On alternating years, plasma levels of total cholesterol, HDL, LDL and VLDL were measured. At baseline, serum cholesterol was collected at the first screening, and plasma cholesterol was collected at the second screening. Lipoprotein subfractions of HDL, LDL, and VLDL were measured from plasma samples. Because there are established analytic discrepancies between plasma and serum total cholesterol values, the MRFIT Group always compared serum values to serum values and plasma values to plasma values.[151]

Blood Pressure Measurement in MRFIT: Blood pressure was recorded annually for the UC group and every four months for the SI group. Four separate blood pressure readings were made at each visit. Systolic blood pressure and diastolic blood pressure were defined as the average of two Korotkoff first- and fifth-phase readings, respectively, obtained with a random-zero sphygmomanometer. The posture of the subject was standardized (seated) and same arm was always used for blood pressure measurement.[152]

Intervention

Men in the UC group received no health messages or intervention from MRFIT staff other than the information that they qualified for the study because

of their high risk for heart disease. They received all medical care on their own, from their usual providers. Many of the members of the UC group received intervention on their cardiovascular risk factors from their usual providers, but such intervention was not documented. Men in the SI group participated in an initial intensive series of group sessions designed to assist in modification of behavior relating to the three risk factors. Subsequently, the SI men were invited back to their clinics at least three times each year to maintain and increase risk factor change.

Intervention on Blood Lipids: The goal of the MRFIT nutrition intervention was to lower the serum cholesterol of all SI men by 10% or more for those with baseline levels of 220 mg/dl or greater (this included the great majority of the men). The food pattern initially taught included saturated fats at a maximum of 10% of calories, polyunsaturated fats at a maximum of 10% of calories, total fat less than 35% of calories, and dietary cholesterol less than 300 mg per day.[151] When initial data collection showed that many men were consuming lower levels of some of these dietary elements, the pattern was changed to specify saturated fat no greater than 8% of calories and cholesterol no more than 250 mg. per day. The dietary intervention was delivered in two phases. The first, intensive phase, consisted of group instruction in the first 10-weeks of participation in the trial. The second phase continued for the remainder of the trial, and consisted of individual nutrition counseling at least every four months. If blood lipids did not respond well, more frequent counseling was done. Consistency of intervention across the 22 centers was accomplished

through centralized national training of local staff members and the use of standardized educational materials at all centers.

The intervention for changing dietary practices used state-of-the-art behavior change principles, still considered appropriate today. Support for behavior change was provided continuously throughout the six years of intervention. Each SI group member was scheduled to meet with a nutrition interventionist a minimum of every four months for the entire six years of the trial.

Intervention on Blood Pressure: [152] A participant was considered hypertensive at screening if his diastolic blood pressure was 90 mm Hg or greater at the third screening visit, confirmed within 4 weeks and/or if he was taking drugs for hypertension treatment. Men who were not categorized as hypertensive at baseline were later designated as hypertensive if their diastolic blood pressure was 90 mm Hg or higher at a regularly-scheduled 4-month visit (confirmed at an additional visit within 4 weeks). Men whose diastolic blood pressure was 115 mm Hg or more at baseline were excluded from the study and advised to get immediate medical attention.

The primary intervention for hypertensives was drug therapy as defined by the Stepped Care Program, employed uniformly at all 22 centers. As described above, overweight men were not started on the Stepped Care Program until weight loss was attempted. When a man was entered into the Stepped Care Program, a goal blood pressure was set for the individual. Antihypertensive drugs were prescribed in a step-wise manner, beginning with a

diuretic and adding more potent medications as necessary to achieve a blood pressure below goal. There were three phases: (1) Step-up, where drug therapy was increased in a step-wise fashion until a satisfactory response was obtained, (2) Maintenance, where no change in the drug was made, and (3) Step-down, where men whose diastolic blood pressure had remained below 80 mm Hg for 4 consecutive visits during maintenance could have a step-wise reduction of medications.

Sodium restriction was also part of the intervention for hypertension. Men were generally instructed to minimize the intake of foods high in sodium content and to use salt sparingly, if at all, in food preparation and at the table. More intensive counseling for sodium restriction was done if a man was taking a maximum dose of Step 2 medication or taking Step 3 medication and the diastolic blood pressure was not below goal.

The diuretics drugs used in the trial, chlorthalidone and hydrochlorothiazide, were found to have a side effect of increasing serum cholesterol.

Intervention on Smoking: At baseline, 63.8% of the men in the MRFIT SI group smoked cigarettes, with an average of 21.5 cigarettes smoked per day. For smokers, the first priority for intervention was smoking cessation. Emphasis was placed on total cessation of smoking, but reduction of dosage by decrease in the number smoked, change in brand, or. reduced inhalation was encouraged for those unsuccessful in quitting. Strong anti-smoking messages were given to all smokers immediately upon their entering the study, at the time of the third

screening visit. Intensive encouragement to stop smoking was provided during the initial 10-week series of group classes. After the first 10 weeks, those who quit smoking were seen on a maintenance basis, and others were placed into an "extended intervention" phase. A number of state-of-the art behavioral techniques were used such as stimulus control, positive reinforcement, contracting, record keeping, and relaxation. Other approaches included retreats, ex-smoker-led groups and special events. Hypnosis and a mild aversive technique were used, following precise protocols.[153]

Intervention on Weight: A basic assumption in protocol development was that reduction in weight for obese individuals would reduce serum cholesterol when dietary lipids composition is low in saturated fat and cholesterol. It was also assumed that weight reduction would reduce blood pressure for some men. There was a goal of ten pound weight loss or more for all men who were overweight. At the beginning of the study, overweight was defined as weight equal to or greater than 1.2 x Ideal Weight. In late 1976, when it was noted that cholesterol levels were not coming down as much as had been anticipated, the definition was revised downward to weight equal to or greater than 1.15 x Ideal Weight. Ideal Weight was defined as 0.9 x the average height-specific weight of men aged 18-34 in the National Health Survey. Note that men whose weight was greater than 1.5 x "Standard Weight" were ineligible for the study.

The "MRFIT diet," which all members of the SI group were advised to follow, included the provision that calories would be adjusted to achieve 1.15

Ideal Weight. In the initial protocol, no emphasis was placed on weight loss, *per se*, except for overweight hypertensives were eligible for a weight reduction program lasting up to 16 weeks in an effort to lower blood pressure before drug therapy begun. [152] It was expected that adherence to the MRFIT eating pattern would result in weight loss for many participants. When it became clear, a couple of years into the trial, that the expected reductions in serum cholesterol were not being achieved, a greater emphasis was placed on weight reduction. In 1975, a set of detailed nutritional and behavioral guidelines on weight control was developed. In 1976, the protocol was changed to allow the recommendation of increased physical activity as a means of controlling body weight.[151]

Physical Activity Intervention: The powerful effect of physical activity on serum cholesterol levels, blood pressure, and weight were not as well-recognized in the 1970's, when the MRFIT study was designed, as it is today. Increasing physical activity was not included in the treatment protocols for hypercholesterolemia or hypertension, but was added to the protocol for weight loss in 1976. The advice was to be limited to recommending an increase in duration but not rate of energy expenditure in currently habitual forms of physical activity. In practice, this meant that most overweight participants were advised to walk more, inasmuch as most of them were habitually sedentary. More ambitious increases in physical activity were neither encouraged nor discouraged, but participants were advised to see their private physicians before embarking on a program of more vigorous activity.[154]

Quality Control on Data Collection

One of the advantages of using the MRFIT data is the quality of the data collected. The MRFIT Study was designed in a national spotlight. The protocols were subjected to intensive review. Because data were collected at 22 different sites around the country, much attention was given to standardization of methods. Uniform training on the protocols was provided by the national coordinating center. Standard forms were used for recording data at all sites. A central lab using only recognized techniques was used.

Specific quality control procedures were developed and implemented for the following:[155]

- Biochemical data at the central lab,
- Forms control and detection of errors in reporting at the Coordinating Center
- Resting electrocardiograms
- Nutrition modalities
- Screening procedures
- Clinic operations
- Blood pressure measurement
- Site visits to clinics.

METHODS

Human Subjects Approval

Approval for the research was obtained from the University Committee on Research Involving Human Subjects. Appendix A includes a copy of the letter of approval.

Obtaining the Data

A Freedom of Information request for the MRFIT data set was submitted to the National Heart Lung and Blood Institute (NHLBI). Appendix B includes the letter approving the request, which lists the conditions that the MRFIT Coordinating Center at the University of Minnesota was not available for extensive assistance and that courtesy copies of any manuscript prepared for publication be submitted to the MRFIT Coordinating Center. The data set was received on 19 tapes - 8 tapes with health information from each of the 8 years of the trial; 4 tapes with physical activity data (collected at baseline and years 1, 4, and 6); and 7 tapes with nutrition data (at baseline and years 1,2,3,5, and 6). Extensive documentation of each data tape was provided, with every version of every data collection instrument used over the 7 years of the study, plus brief descriptions of every variable on each tape.

Extraction of Data Needed for Analysis

The data set documentation was examined to discern what data elements were available. Over 1,000 data elements for each subject were identified as necessary to answer the research question. Computer programs using SAS software (SAS Institute, Inc.[156]) were written to allow extraction of the needed variables from each data tape, using the Michigan State University mainframe IBM computer. Each program was designed to locate the variables of interest on the data tape, copy them from the data tape into a SAS data set suitable for analysis by personal computer and give each variable a new name. The data sets created in this manner were then sorted by subject identification number, and combined as needed at each stage of data analysis. See Appendix C for a sample of a successful SAS program for data extraction.

"Cleaning" the Data

Checking for Inaccuracies in the Data Set: The data set was checked for inaccuracies in several ways. First, all variables for the initial 50 subjects were printed out and visually inspected to determine whether values reported for each variable were feasible. Second, for each variable, descriptive statistics were generated, including mean, range, minimum and maximum values; these were evaluated for feasibility.

Identifying Infeasible Weight Data: One of the most critical phases of data analysis was making decisions about extreme values for weight measurements. Extreme weight changes which actually did occur were of the greatest importance for the proposed research. However, extreme weight values

that were the result of measurement or coding errors would introduce random error which would increase the chance of a Type II statistical error (failing to find a difference when one really was present). Criteria for detecting infeasible weight measurements were developed separately for the four-month weight changes documented in the SI Group and for the twelve-month weight changes documented in the UC Group.

Infeasible 4-month Weight Changes: For weight changes in the SI Group, documented every four months, a review of the literature was done to determine the maximum biologically-possible weight loss and weight gain for men over a 4-month interval.

For weight loss, a national multi-center evaluation of the Optifast program[157] was chosen as suitable for estimation of a maximum biologically-feasible rate of weight loss. The men in the Optifast program were considerably heavier than the MRFIT subjects and experienced considerably greater caloric restriction than the MRFIT SI Group were likely to have seen. The mean weight loss in four months observed in the Optifast subjects could reasonably be considered a biological maximum for the purpose of this research. For weight gain, three studies of purposeful weight gain in human males were found,[66, 158,159] in which overfeeding resulted in weight gains of 16-25.5% of baseline weight in four months. Based on these four studies, it was concluded that a weight loss or gain of approximately 20% would represent the maximum biologically-feasible weight change in a four-month interval. Table 4 summarizes the findings of the relevant studies.

Table 4 - Summary of Studies of Weight Change in Males Under Extreme Conditions of Overfeeding and Underfeeding

Population	N	Mean Age, Years	Initial Mean Wt.	Weight Change in 4 Months, (Per Cent of Body Weight)
Men from 18 Optifast Clinics[157]	110	42.3	128.7 Kg.	Loss of 22%
Male Canadian Twins [66]	24	21	60.3 Kg.	Gain of 16-22%
Vermont Prisoners[158]	9	24.8	Not Reported	Gain of 19%
Males, Fattening Ritual in N. Cameroon[159]	9	23-25	68.5 Kg.	Gain of 25.5%

Even with the literature review described above, defining the criteria for infeasible weights in the data set was still a somewhat arbitrary process. On one hand, the MRFIT participants were not subjected to the extreme caloric restriction that Optifast patients had experienced. On the other hand, weight regain in an overweight person following a period of calorie-restricted dieting for weight loss could be much more rapid than weight gain in a slender person caused by overfeeding. The decision was made to define infeasible weight changes in the MRFIT as follows: A weight was considered infeasible if that weight represented a change greater than 15% of body weight in one 4-month interval and if that weight were also more than 1.96 standard deviations above or below the subject's mean weight over the course of the trial.

There were 107 men in the SI group who had weights meeting these criteria. To verify that the criteria were appropriate, plots were made of weight on time for 16 of the 107 subjects, selected at random, which supported the

criteria. One additional check on the 107 infeasible weights was made. For each subject with a weight considered infeasible, a printout was obtained of all weights and all corresponding blood pressures. Since blood pressure is very responsive to changes in weight, patterns of change in blood pressure were examined for consistency with patterns of change in weight. This closer examination revealed that only 95 weights were truly infeasible, and each of these was re-defined as a missing value.

Infeasible 12-month Weight Changes: To identify infeasible weights for the UC group, where weights were recorded only on an annual basis, it was not possible to find in the literature studies reflective of maximum biologically-feasible weight gain or loss over a twelve-month period. Since a weight gain of 15% in 4 months identified outliers in the SI group, it seemed obvious that an infeasible per cent weight change in a year should be defined at higher than 15%. On the other hand, the UC Group did not receive the intense encouragement to lose weight that the SI Group was given by the MRFIT staff, so a lower cut off for infeasible weight change may have been appropriate. A trial and error approach was used to define exclusion criteria: Several criteria were applied, and were then verified by plots of weight on time for a sample of subjects found to have infeasible weights by each criteria.

Using this method, the criteria for exclusion for the UC Group finally adopted were that a weight was considered infeasible if that weight represented a change of 25% in a one-year interval and that weight was more than 1.96 standard deviations from subject's mean weight. When these criteria were

applied, 46 weights were identified as infeasible, and were re-defined as missing data.

Dealing with Missing Weight Data

The next step in preparing the data for initial analyses was deciding how much missing weight data would be tolerated before a subject was excluded from analyses. A program to quantify the patterns and numbers of non-missing weights was developed.

Dropping Year 7 Data: As expected, the longer participants were in the study, the more missed visits were observed. By the time of the year 7 annual visit, 7,500 of the initial 12,866 subjects did not have weight data, and most of these were also missing cholesterol and blood pressure measurements. The decision was made to consider the data collected at the year 6 annual visit to be the "final" measurements for the purpose of this study. For the outcome variables HDL and the ratio of total plasma cholesterol to HDL, year 6 was, in fact, the last year that this information was documented. To assess how results might have differed if the year 7 data had been retained as the final date of weight measurement, subjects who were present at year 7 were compared with those absent at year 7 in terms of several characteristics (ANOVA, with post hoc test Bonferroni Inequality). See Table 32 for a summary of these comparisons.

Identifying Subjects with "Enough" Data: For the 4-month interval weights measured in the SI Group, 3,510 subjects had a complete set of 19 weights, 841 subjects were missing only one weight, 425 subjects were missing two weights, and 236 were missing three weights. It was arbitrarily decided that

a subject missing more than 3 weights would be excluded from analysis. One additional criterion was added in identifying subjects with enough data for analysis - the subject needed to have the weight measured at the year 6 annual visit, which was the weight used to define the summary variable "net weight change." When the double criteria of having at least 16 valid weights and also having the year 6 annual weight, 4,932 SI subjects remained for analysis.

For annual visit weights only, 10,039 subjects had a complete set of 7 weights, 1,101 were missing one annual weight, and 1,726 were missing two or more weights. It was arbitrarily decided that only subjects with a complete set of 7 annual weights would be retained for analysis, resulting in a data set with 10,039 individuals. To assess possible bias from dropping individuals with missing data, T tests were run, comparing subjects dropped with those who has "enough" data. Table 33 summarizes these comparisons.

Replacing Missing Weight Values

The few missing weights left in the SI data set were replaced with calculated estimates of the missing weight. Two possible computations were considered:

1. The missing weight could have been replaced by the subject's mean weight over the course of the trial. This commonly-accepted method for replacing missing values was rejected because it could result in overestimation of a subject's number of weight cycles and the magnitude of the residuals for the regressions of weight on time.

2. The missing weight could have been replaced by the average of the weight preceding and the weight following the missing value. Given that the weight measurements were taken at such short intervals, this method was considered most appropriate.

Creating Summary Variables Suitable for Statistical Analysis

A number of decisions were made as to how to quantify the data available in ways which would meaningfully reflect factors potentially affecting changes in blood pressure and changes in blood lipids. The decision-making process for each category of information is described below.

Outcome Variables: The outcome variables defined for this research were changes in the cardiovascular risk factors: total serum cholesterol, HDL, the ratio of total cholesterol to HDL and diastolic blood pressure. Note that the ratio of total cholesterol to HDL was based on total plasma cholesterol rather than total serum cholesterol, because the laboratory HDL measurements were based on samples of blood plasma rather than blood serum. The value for baseline blood pressure was the value defined by MRFIT staff, which was the average of four diastolic blood pressure measurements taken with a random-zero sphygmomanometer - two at the second screening visit, and two at the third screening visit. The value for the year 6 blood pressure was the average of two diastolic blood pressure measurements taken with a random-zero sphygmomanometer at the year 6 annual exam. In each case, the change in risk factor was defined as the difference between the value at the year 6 annual exam and the value at baseline.

Predictor Variables: For this study, two different definitions of weight cycling were used, plus a third which was a combination of the other two. For each potential definition of weight cycling, plots of weight on time for a sample of subjects was generated, to determine whether the weight cycling variables created by mathematical definition corresponded to intuitive understanding of weight cycling. The three measures of weight cycling were as follows.

1. **Number of Cycles:** where a weight cycle was defined as a loss and subsequent regain (or gain and subsequent loss) of at least 5% of baseline weight. The decision to use 5% of weight as the minimum change to define a cycle was based on the finding by Blair et al.[1] that, in the MRFIT population, men who had undergone at least one 5% weight cycle had a 55% increase in all-cause mortality compared with stable-weight subjects. The original SAS program written by Jay McClellan to count the number of weight cycles is found in Appendix D. In order to compare the results of this study to the results of the mortality study of Blair et al.[1], some ANCOVA models were created where the number of cycles was expressed in terms of "cycling status," where a subject with no cycles was classified as a "non-cycler," and an individual with one or more cycles was classified as a "cycler."
2. **SEE:** The standard error of the estimate of the regression of each individual's weight on time was selected over the standard deviation of weight (used in most other weight cycling studies) because steady weight

losses and gains can result in a high standard deviation of weight when no weight cycles occurred.

3. **Number / Size of Cycles:** In order to explore the potential impact of small weight cycles compared to large weight cycles, a third measure of weight cycling was developed, reflective of both the number and size of the weight cycles, which combined the previous two cycling measures. An individual with a low SEE (below the median SEE for the entire population) was assumed to have smaller cycles than a person with a large SEE. For the third measure of weight cycling, individuals were classified into the following groups:

    1. Zero cycles
    2. 1 cycle, low SEE (<4.5 pounds)
    3. 1 cycle, high SEE (≥4.5 pounds)
    4. 2 cycles, low SEE (<4.5 pounds)
    5. 2 cycles, high SEE (≥4.5 pounds)
    6. 3 or more cycles.

Individuals with 3 or more weight cycles were not subdivided by magnitude of SEE because only 34 of the 260 subjects with 3 or more weight cycles had a low SEE. The third measure of weight cycling was used only in ANCOVA models.

Adequacy of 12-Month Interval Data for Describing Weight Cycling

The weight measurements recorded at 4-month intervals over a 6-year period for the MRFIT SI Group constitute a remarkably complete documentation of weight changes in a large population over time. The number of weight cycles and the SEE calculated for the SI population based on 19 four-month interval weights could be considered reliable estimates of weight cycling.

Before statistical analysis was begun, the question of how well the 7 weights documented at annual visits for all 10,039 subjects would describe the "true" weight patterns based on 19 weights, known for the 4,931 members of the SI Group. If weight cycling could be adequately characterized by 7 weights, all 10,039 subjects could be used in data analysis. To answer this question, the "true" measures of weight cycling (based on 19 weights) were compared with the measures based on only 7 weights, as follow.

The number of weight cycles and the SEE were calculated for each member of the SI group, first using all 19 validated weights taken at 4-month intervals, and then using only the 7 validated weights taken at 1-year intervals. It was found that restricting the weight data to only annual measurements resulted in underestimation of the number of weight cycles in 54.2% of subjects, and also resulted in discrepancies in the SEE (Pearson correlation coefficients for SEE based on 7 weights and SEE based on all 19 weights was 0.90). Because of these discrepancies, the decision was made to perform statistical tests only on the SI Group, where confidence in the data was highest. To assess potential bias from dropping the UC group from analysis, T tests were run comparing the

UC and SI groups with respect to the baseline characteristics age, weight, relative weight, blood pressure, total cholesterol, HDL, and LDL (See Table 34.).

Other Independent Variables Created for Possible Inclusion in Analyses

Nutrition Variables: Nutrition information available for analysis in the data set were the results of 24-hour dietary recalls recorded by highly trained dietitians, taken at baseline and at years 1,2,3,5, and 6. Based on review of literature on nutrients and heart disease, nutrients suspected of affecting blood lipids and blood pressure were identified. SAS programs were written to extract 24-hour intakes of the following from the nutrition data tapes: grams of fat, saturated fatty acids, polyunsaturated fatty acids, alcohol and water-soluble fiber; calories; milligrams of cholesterol, calcium, iron, sodium, and caffeine; and international units of vitamin E.

Typical intakes of these nutrients over the trial were defined as follows. Baseline intake data were not considered representative of intake over the trial, because the most intensive dietary intervention was done between the screening visits where baseline data were collected, and the first annual visit. Mean intakes over the three consecutive years for which food intake data were available (years 1, 2, and 3) were calculated for each subject for each of the extracted nutrients. Values for calories, fat, saturated fat, and polyunsaturated fat were used to calculate the summary variables mean per cent of calories from fat and mean ratio of polyunsaturated to saturated fat (P:S ratio). If subjects did not have at least two of the three 24-hour dietary recalls, the mean values for all nutrients were defined as missing and not used in analysis.

Pearson correlation coefficients between each nutrient intake variable and the outcome variables were very low, seldom reaching 0.1, and often failed to reach statistical significance (See Appendix E). For each analytic model, all nutrition intake measures that were correlated significantly with the outcome were included in analysis.

In addition to the actual nutrient intake data, one additional nutrition variable was extracted from the data set - the dietitian's rating of dietary compliance, based on impressions made during dietary counseling. In the early MRFIT publications,[151] the dietitian's rating of dietary compliance was the nutrition variable found to correlate most highly with changes in blood cholesterol and blood pressure. This same high correlation was found between compliance rating and outcomes in these data; however, the variable was discarded from analysis when it was learned, from personal communication with former MRFIT nutritionists, that laboratory values for cholesterol and blood pressure were taken into account by the dietitians when they made their assessment of dietary compliance.

Smoking-related Variables: The serum thiocyanate level used as a cut-off to verify smoking status was 100 micromoles per liter, consistent with other analyses based on this data set and officially published by the MRFIT Research Group.[153]

For this analysis, subjects were classified as non-smokers during the trial if, at baseline screening and at each annual visit, the subject reported being a non-smoker and, in addition, his serum thiocyanate level at each visit was less

than 100 micromoles per liter. A continuous smoker was defined as one who, at each annual visit either reported being a smoker, or had a serum thiocyanate level greater than or equal to 100 micromoles per liter. An intermittent smoker was defined as one who was verified to be a non-smoker at least one visit and who was verified to be a smoker at least one other visit.

To quantify the amount of smoking, the mean number of cigarettes per day over the trial was calculated, as was the sum of the number of cigarettes smoked. Number of cigarettes per day and smoking status at the time of the final visit were also considered for inclusion in the analysis because the effects of smoking on blood pressure are seen at the time the smoking is occurring and shortly thereafter.[152]

Smoking cessation has been shown to be associated with weight gain,[146] and individuals who quit and resumed smoking several times would be likely to have experienced weight fluctuations. Two measures reflective of quitting smoking were calculated. One was the per cent of annual visits at which the subject was judged to be a smoker (based on self-report and serum thiocyanate values). The other variable reflective of changes in smoking habits was the standard deviation of the number of cigarettes reported.

Of the smoking-related variables, the most highly correlated with outcomes were the mean number of cigarettes/day over the entire trial and smoking status during the trial. These were highly correlated with one another ($r=0.55$), and were not ever included in the same model. Mean number of cigarettes/day was included in every model submitted.

Physical Activity Variables: Several variables reflecting physical activity and physical fitness were chosen. In the MRFIT, physical activity was documented by means of leisure time physical activity scores (LTPA). It has been established by the MRFIT Research Group that LTPA scores remained relatively constant from Annual Visit 1 through Annual Visit 6.[160] Therefore LTPA scores for Annual Visit 1 were extracted from the data set for inclusion in the study. On the MRFIT data tapes, physical activity information is summarized as average minutes per day of light, moderate, and heavy LTPA, the sum of which is the total minutes of LTPA. For this research, the primary measure of physical activity chosen for inclusion was total minutes of LTPA, because that variable had been found to best predict CVD and all-cause mortality in the MRFIT population.[160] Average minutes per day of heavy LTPA was also included.

For analysis, LTPA was expressed in several ways. Some subjects were found to have infeasibly high LTPA scores. It was assumed that men whose total LTPA scores were unrealistically high were likely to be those who performed a larger number of activities, and may have been among the more physically active subjects in the trial. To avoid eliminating the most physically-active subjects from the study, subjects were classified by quintile for minutes of LTPA. Additional variables were created where the LTPA scores of subjects with more than 10 hours per day of LTPA were re-defined as missing values.

Altogether, 8 variables reflecting amount of physical activity were created: total minutes of LTPA , total minutes of heavy LTPA, quintile of total LTPA,

quintile of heavy LTPA, plus expurgated versions of each of those 4 variables where any values greater than 10 hours/day were redefined as missing. Correlations between each of the 8 physical activity variables and the outcome variables were very low (always less than 0.1), and seldom reached statistical significance. For each analytic model, if any of the 8 physical activity measures was correlated significantly with outcome, it was included in analysis.

Another measure of habitual physical activity pattern available in the data set was the participant's opinion of his own physical activity compared to others his age. Exercise opinion changed from one year to the next in most subjects. Therefore, three different measures of exercise opinion were created: mean exercise opinion over years 1-6 of the trial, average of the last two reported opinions and the exercise opinion at the final visit. Of these three measures, exercise opinion at the final year 6 visit correlated most highly with outcomes, so this was used in analysis.

Physical Fitness Variable: Physical fitness level and physical activity level are correlated in individuals but not identical. For this analysis, exercise duration at baseline was used as the only measure of physical fitness. Exercise duration in subsequent years was not available in the data set. Exercise duration was significantly correlated with changes in blood pressure, but not with changes in blood lipids, so was included only in models related to changes in blood pressure.

Medical Conditions and Medications At baseline and at each annual anniversary, all MRFIT subjects were given thorough medical examinations,

including an extensive medical history and inventory of medication use. Conditions and medications which could affect weight, blood pressure, or cholesterol were considered in this analysis, as described below.

■ **Conditions Affecting Weight:** Many conditions and medications can potentially cause increases or decreases in weight. Of the conditions and medications documented in the MRFIT data set, the following were initially identified as having potential effects on weight: diabetes, hyper- or hypothyroidism, Cushing's disease, primary aldosteronism, nephritis/nephrosis, congestive heart failure, alcoholism, drug addiction, depression, chronic obstructive lung disease, tuberculosis, peptic ulcer, gall bladder disease, cirrhosis and other liver diseases, anemia, lymphadenopathy, reporting black or tarry stools, stroke, malignant neoplasms, reserpine, prazosin, cholestyramine, nicotinic acid, insulin or oral hypoglycemic agents, steroids, digitalis, spironolactone, hydralazine, dextrothyroxine, allopurinol, amphetamines and other stimulants. Thirty-eight per cent of subjects had one of these conditions or drugs at some point during the study. This was considered too much of the sample to exclude from analysis, so the subjects with any of these conditions or medications were identified in a variable RXDXWT (0=no, 1=yes), and this variable was included in regression models.

In final analyses, only conditions judged to have the most dramatic effects on weight served as the basis for exclusions, including cancer, Cushing's disease, hyper- or hypothyroidism, and pheochromocytoma.

■ **Conditions Affecting Blood Pressure:** Of the conditions and medications documented in the MRFIT data set, the following were identified as having potential effects on blood pressure: angina pectoris, stroke, peripheral arterial occlusion, pulmonary embolism, thrombophlebitis, atrial fibrillation, other arrhythmias, pheochromocytoma, primary aldosteronism, alcoholism, and drug addiction. In the SI group, 831 subjects (17%) had one or more of these conditions. Subjects with any of these condition were identified in a variable BPUPDX (0=no, 1=yes), and this variable was included in regression models. Only conditions judged as having the most drastic effects on blood pressure were used to exclude subjects, including angina, renal disease and primary aldosteronism.

■ **Medications Affecting Blood Pressure:** Eighty-nine per cent of SI subjects took antihypertensive drugs at some point during the study. This factor was taken into account in ANCOVA analyses by blocking, in some models, on use of antihypertensive drugs.

■ **Conditions Affecting Cholesterol:** Conditions known to significantly affect cholesterol were identified, to allow control for these conditions in models predicting change in blood lipids. The two conditions thus identified were diabetes (defined either by a diagnosis of diabetes, use of insulin or oral hypoglycemic agents, or at least 2 fasting serum glucose concentrations greater than 140 mg/dl[161] during the final 2 years of the trial) and liver disease.

■ **Use of Cholesterol-lowering Drugs:** One hundred seventy-six subjects (4% of the SI Group) were using cholesterol-lowering drugs at some

time during the trial. A variable was created to identify subjects who had taken cholesterol-lowering drugs, and these subjects were excluded in some ANCOVA models.

- **Use of Cholesterol-raising Diuretics:** Two of the diuretics used in the MRFIT protocol for lowering blood pressure (chlorthalidone and hydrothiazide) had a side effect of raising total cholesterol. Almost half of the SI subjects were taking one or another of these drugs at some point throughout the study, and were identified so this factor could be controlled in data analysis.

Mental Health Measures: Review of several published studies of mental health status and subsequent mortality in the MRFIT cohort revealed that none of the variables available in the data set were correlated with subsequent mortality. Therefore, no mental health variables were included in analysis.

Variables Related to Weight Change Three variables were created to describe the weight changes most likely to affect changes in blood lipids or blood pressure: (1) net weight change from baseline to year 6, (2) weight change in the final 1-year interval, and (3) weight change in the final 4-month interval before the year 6 visit. When correlations between the outcome measures and all of the created variables were examined, it was found that the one variable most highly correlated with outcomes (aside from baseline values for each outcome measure), was net weight change. (See Tables 35-38, Appendix E.) Net weight change had also been shown by Blair et al. to predict mortality in the MRFIT population[1].

Creation of net weight change groups: To facilitate comparisons between weight cycling's effects on risk factors and its effect on mortality, subjects were divided into 3 groups by net weight change between baseline and the year 6 annual visit. The weight loss group included subjects who had lost more than 5% of baseline weight. The no change group included those whose weight changed less than 5% from baseline, and the weight gain group gained more than 5% of baseline weight. Close examination of relationships among variables were showed that the three net weight change groups were significantly different from one another with respect to all outcome variables (Table 9), most baseline variables (Table 6), and almost all the variables used in analysis (Table 10). Differences in means were compared by Analysis of Variance (ANOVA), using the Bonferroni Inequality test for post hoc comparisons.

Because the net weight change groups were different from one another in so many respects, the decision was made to perform all statistical tests on the whole population and also separately for each net weight change group.

Statistical Approaches

Statistical analysis was done using the SAS System for Microsoft Windows, Release 6.10,[156] licensed to Michigan State University. Two primary statistical approaches were used to test the hypotheses - analysis of covariance (ANCOVA) and multiple regression. ANCOVA allowed comparisons of mean changes in blood pressure and blood lipids by each measure of weight cycling, while controlling for variables thought to affect the outcomes. The output of

ANCOVA models allowed an easily-interpretable examination for any potential dose-response effects from weight cycling.

Stepwise multiple regression was used in addition to ANCOVA to take advantage of more extensive control for the variables thought to affect the outcomes. With multiple regression, the effect of each predictor variable is made more certain because the possibility of distorting influences from other independent variables is removed.[162]

In addition to the two primary statistical approaches described above, a preliminary analysis was done using ANOVA on small homogeneous weight groups.

The alpha level chosen for determining statistical significance for this research was 0.05.

Exclusions

There were initially 6,428 subjects in the SI Group. Subjects were excluded from analysis for the following reasons:

1. Inadequate data: As described earlier, 1,496 subjects without at least 16 of 19 possible weight measurements were excluded from analysis. This left 4,932 subjects.
2. Medical conditions affecting weight: For all analyses, individuals with conditions affecting weight drastically were excluded, including 235 subjects with cancer or "unexplained weight loss" (assumed to be cancer), and 31 with hyper-or hypothyroidism. No subjects were found to have the other two conditions marked for exclusion - Cushing's syndrome or

pheochromocytoma. Three of the subjects excluded for these reasons had more than one condition; 4,669 subjects remained.

3. Medical conditions affecting blood pressure: For analyses related to changes in blood pressure, subjects with conditions known to drastically affect blood pressure were excluded, including 9 with renal disease, 284 with angina and 1 with primary aldosteronism. Some of the subjects excluded for these reasons had more than one condition; 4,393 subjects remained available for blood pressure-related analyses.

4. Medical conditions affecting blood lipids: For analyses related to changes in total cholesterol, HDL and the ratio of total cholesterol to HDL, subjects with conditions likely to drastically affect cholesterol were excluded, including 346 diabetics, and 49 with cirrhosis and other liver diseases. Some of the subjects excluded for these conditions had both conditions; 4,302 subjects remained for blood lipid-related analyses.

Sample Size / Power

Minimum differences in outcomes that would have to have been observed to conclude that weight cyclers were different from non-cyclers were calculated, using the formula for a 2-sample z-test (below), and solving for the difference between means:

$$z = \frac{(\bar{x}_1 - \bar{x}_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Based on this calculation, the sample size was large enough to detect at the alpha = .05 level the following differences in outcomes between cyclers and non-cyclers: 2.6 mg/dl for total cholesterol, 0.73 mg/dl for HDL, 0.12 for the ratio of total cholesterol to HDL, and 0.76 mm of Hg. for blood pressure.

Deciding Which Possible Variables to Include in Statistical Analysis

Correlation with Outcome: Once all the possible covariates were extracted from the data tapes, summarized, and re-coded as appropriate, correlation analysis was done to see which of the variables available were statistically related to each outcome measure. Correlations of each independent variable with each outcome variable were checked not only in the entire non-excluded population, but also in each net weight change subgroup. These checks were done separately for the non-excluded population for blood lipid analysis and for the non-excluded population for blood pressure analysis. Only the variables significantly correlated with each outcome variable in the population group or subgroup being examined were included in ANCOVA or regression models involving that outcome measure. See Tables 35-38 in Appendix E for a summary of selected correlations.

Eliminating Multicollinearity: The next stage in selection of variables was to eliminate any possibility of multicollinearity clouding interpretation of the

results. Multicollinearity occurs when two independent variables are highly correlated with one another and also with the outcome variable. When multicollinearity is present, parameter estimates become unreliable.

In order to eliminate the possibility of multicollinearity, consideration of the correlation of each variable with every other variable in the data set was done, as follows. Once it was determined which variables were statistically associated with each outcome measure, matrices were generated showing the correlation of each potential covariate with every other covariate. Eight separate matrices were generated and checked for possible multicollinearity - four based on the non-excluded population for blood lipid models (for the entire population and for each of the 3 net weight change subgroups) and the same four for the non-excluded population for blood pressure analyses. Each Pearson correlation coefficient was checked. High correlations were found among three weight variables - baseline weight, relative weight at baseline, and mean weight over the course of the trial. Similarly, there were high correlations between total minutes of leisure time physical activity and total minutes of heavy physical activity, between baseline HDL and baseline ratio of total cholesterol to HDL, and between mean number of cigarettes smoked and total number of cigarettes smoked.

In each of the above instances, decisions had to made regarding which of the related variables to include in models. The decisions were based on the degree of correlation with the outcome and on which made the most theoretical sense.

Consistency of Correlation Across Net Weight Change Subgroups: For ANCOVA models only, there was one additional criterion for selection of variables. ANCOVA models based on the entire non-excluded population which blocked on net weight change group included only variables found to be significantly correlated with the outcome in all three net weight change groups. This limitation was considered necessary because ANCOVA controls for covariates by holding them at their mean value, with the assumption that the regression of the outcome variable on the covariate is the same within the treatment groups.[163]

Tables 35-38 in Appendix E demonstrate the basis for selection of variables for inclusion in various models. They show patterns of correlations of selected variables with outcomes, for the entire non-excluded population as well as for the each net weight change group. Variables consistently correlated with outcomes across all net weight change subgroups are highlighted by shading.

Preliminary Analysis: ANOVA for Homogeneous Weight Groups

Because weight changes were observed to be so highly predictive of changes in blood lipids and blood pressure, a preliminary statistical analysis was done in an attempt to completely eliminate whatever effects baseline weight and net weight change might be exerting on outcomes.

Three subgroups were identified, each of which was similar in terms of baseline weight (within 5 pounds of median baseline weight for that group) and net weight change (within 5 or 6 pounds of median weight change for that group). In order to keep the groups homogeneous, only the approximately 50 subjects meeting the criteria for each group were included. Table 5 shows the characteristics of the homogeneous weight groups.

Table 5 - Characteristics of Homogeneous Weight Groups

Net Weight Change Group	Baseline Weight, lb	Net Weight Change, lb	Non-excluded Population for Blood Pressure Analyses n	Non-excluded Population for Cholesterol Analyses n
Loss	189.5 to 194.5	-13 to -7	51	48
No Change	182.5 to 187.5	-2.5 to 2.5	52	49
Gain	182 to 187	3 to 9	53	51

For each of the three homogeneous subgroups, the SAS GLM procedure was used to perform ANOVA to test whether cycling status, the number of weight cycles, or the tertile of SEE contributed significantly to the variability in changes in total cholesterol and changes in blood pressure. For these analyses, the number of weight cycles was re-defined, combining those with 3 or more cycles

with those with 2 cycles, so that each cell would have at least 6 subjects. The SAS MEANS procedure was used to calculate mean changes in each outcome by each measure of weight cycling. To determine whether the mean outcomes were significantly different from one another, the post hoc multiple comparison procedures used were the Scheffe and Bonferroni Inequality tests. In addition, 95% confidence intervals were calculated for each mean change in outcome, and are reported in Table 31.

Analysis of Covariance Models

The SAS GLM procedure was used to perform ANCOVA, which tested whether weight cycling measures contributed significantly to the variability in changes in blood lipids and blood pressure, with adjustments for covariates. The null hypothesis tested in ANCOVA is that the mean change in outcome by each measure of weight cycling is the same. Covariates are the continuous variables which are measures of factors thought to exert independent influences on the outcomes. The SAS LSM procedure was used to calculate least square mean changes in each outcome by each measure of weight cycling. Least square means are the expected values of means that would be expected for a balanced design involving class variables with all the covariates at their mean values.[156] To determine whether the least square mean outcomes were different from one another, an alpha level of 0.05 was chosen. The 95% confidence intervals were calculated for each adjusted mean change in outcome, and are presented in Tables 11-26.

For ANCOVA models, the weight cycling measures were class variables, expressed as four different categorical variables - (1) cycling status (non-cycler vs. cycler), (2) number of cycles, (3) tertile of SEE, and (4) number / size of cycles.

Models Using Entire Non-excluded Population: Despite known differences among the net weight change groups, it was desirable to create models based on the whole population, blocking on net weight change group, so that the larger number of observations could maximize the power of the statistical tests. However, because of the differences in characteristics among the three weight change groups, only the few variables significantly correlated with the outcomes in all 3 subgroups were used in the models (See Tables 35-38 in Appendix E). Independent variables meeting the selection criteria for inclusion as covariates for the models based on the entire non-excluded populations are listed below.

- Net change in total cholesterol: baseline cholesterol, the mean ratio of polyunsaturated to saturated fats (P:S), and the mean number of cigarettes/day reported over the trial.
- Net change in HDL: baseline HDL, mean intake of caffeine per day, and mean number of cigarettes/day. Mean intake of alcohol per day was also included in the HDL models because of the known effect of alcohol on HDL.
- Net change in the ratio of total cholesterol to HDL: baseline plasma cholesterol, baseline HDL, and mean caffeine intake. Note that mean number of

cigarettes/day did not meet the criteria for inclusion in the model for cholesterol ratio, but was included to make the model consistent with other models.

- Net change in blood pressure: baseline blood pressure, and mean number of cigarettes per day. Note that in the models for change in blood pressure, there was a statistically significant interaction between net weight change group and each cycling variable, so only models based on weight change subgroups could be evaluated.

Although race was not significantly correlated with the outcome in either the entire non-excluded population or any subgroup, it was initially included in ANCOVA models to verify that the findings did not differ by race. There was no interaction of race with any measure of weight cycling in any of the models of blood lipids. In blood pressure models, however, significant interactions with race were noted in two models, necessitating separate analyses by race.

Models Using Net Weight Change Subgroups: In models based on the net weight change subgroups, all variables significantly correlated with change in outcome within the particular weight subgroup were included. As can be seen in Tables 35-38 in Appendix E, each weight group had a somewhat different group of variables which were significantly correlated with the outcomes, so each model was somewhat different. Tables 11-26 clearly specify which variables were included in the original models, and which were found to contribute significantly to the model. Only those which contributed significantly to the model were included in the final versions where adjusted mean outcomes were calculated.

Summary of Primary ANCOVA Models: In summary, for each of the four outcomes being examined in this research, there were 4 basic models developed - one for each population group. Each of the 4 basic models included the same variables - the ones correlated with the outcome in that population group. Each basic model was repeated four times, substituting a different measure of weight cycling each time. Figure 1 summarizes the 16 resulting primary ANCOVA models. Each of the 16 models so developed was re-submitted with additional controls, as explained below.

Population	Cycler vs. Non-Cycler	Number of Cycles	Tertile of SEE	Number / Size of Cycles
All Non-excluded	Model 1A	Model 1B	Model 1C	Model 1D
Weight Loss Group	Model 2A	Model 2B	Model 2C	Model 2D
Weight No Change Group	Model 3A	Model 3B	Model 3C	Model 3D
Weight Gain Group	Model 4A	Model 4B	Model 4C	Model 4D

Figure 1 - Summary of the Sixteen Primary ANCOVA Models Submitted for Each of the Four Outcomes of the Research

Additional Controls for ANCOVA Models

Some of the variables reflective of factors expected to affect changes in blood lipids and blood pressure were categorical variables which could not be included in initial ANCOVA models because inclusion would have resulted in subgroups with no subjects. For example, if blocking were done on net weight group (3 levels), number of weight cycles (4 levels), race (2 levels), and smoking

status (3 levels), SAS would have computed comparisons among 72 subgroups, some of which would have no subjects within them. In general, it was not possible to block on more than 3 class variables in ANCOVA models.

In order to incorporate into the analysis the information contained in theoretically important categorical variables, some ANCOVA models were repeated with different categorical variables when race was shown to make insignificant contributions to the explanatory power of the models. These additional controls are described below.

- **Additional Controls for Smoking:** Number of cigarettes per day was not found to contribute significantly to total cholesterol Models 1A - 1D. To be sure that smoking was not somehow confounding the results, each of these 4 models was repeated, stratifying on only the cycling variable and on smoking status during the trial.

- **Additional Controls for Exercise:** Several models for total cholesterol, blood pressure, and HDL in which the continuous variables reflective of physical activity or fitness did not contribute significantly to the model were repeated, blocking on exercise opinion at year 6 or quintile of physical activity (whichever of the two was most highly correlated with the outcome in the population subgroup being examined).

- **Additional Controls for Use of Diuretics Which Raised Cholesterol:** All ANCOVA models for total cholesterol and HDL were repeated blocking on use of lipid-raising diuretics during the final two years of the study.

■ **Additional Controls for Use of Cholesterol-lowering Drugs:** One hundred seventy-six subjects (4%) of the SI Group were using cholesterol-lowering drugs at some time during the trial. It was not possible to control for this variable by blocking on it because the small number of subjects resulted in empty cells. To rule out the possibility that these drugs were confounding the analysis, all total cholesterol and HDL models were repeated, excluding from analysis all subjects who had taken a cholesterol-lowering drug at any time during the trial.

■ **Additional Controls for Use of Antihypertensive Drugs:** The vast majority of hypertensive subjects (83%) were prescribed antihypertensive drugs. To rule out the possibility that antihypertensive drug use was obscuring an effect of weight cycling, all blood pressure models were repeated, blocking on use of these drugs.

■ **Additional Controls for Baseline BMI:** Blair et al.[1] found that weight cycling was associated with increased mortality only in the MRFIT participants who were at normal weight or who were moderately overweight. For men who were the heaviest at baseline, weight cycling was not associated with increased mortality. To rule out the possibility that weight cycling may be affecting risk factors differently for heavy men, ANCOVA models for changes in total cholesterol and blood pressure were repeated, blocking on tertile of baseline BMI.

Regression Analysis

Stepwise multiple regression models were developed for each outcome to test the null hypothesis that the partial slope estimate for each measures of weight cycling was 0. In SAS, stepwise regression begins with no variables in the model. For each of the independent variables submitted in the model, SAS calculates an F statistic that reflects that variable's contribution to the model if it were to be included. Variables are added one by one to the model, starting with the variable that results in the largest F statistic for the model. The selection criterion for inclusion of a variable in a model is that the F statistic for a variable have a p value <.50. (Note that variable selection is an exploratory rather than confirmatory process. The significance level required for inclusion in the model does not have the same connotation as the significance level required for rejecting the null hypothesis about the partial slope estimate. The p value required for inclusion in the model is higher than the p value required for rejecting the null hypothesis.) After a variable is added, the stepwise method looks at the variables already included in the model and deletes any variable that no longer produces an F statistic significant at p<.5 level. Only after this check is made and the necessary deletions accomplished is another variable added to the model. The stepwise process ends when none of the variables outside the model has an F statistic significant at the p<.5 level, and every variable in the model is significant at the p<.5 level.[156]

In testing the hypothesis that the partial slope estimate for each measure of weight cycling was 0, an alpha level of 0.05 was used. Ninety-five per cent

confidence intervals were calculated for each partial slope estimate, and are included in Tables 27-30.

Measures of Weight Cycling Used: For the regression analyses, SEE was used as a continuous variable, and the number of cycles were expressed as a series of 3 dummy variables:

- CYCDUM1: 0= no cycles, 1=1 or more cycles
- CYCDUM2: 0= 0 or 1 cycles, 1= 2 or more cycles
- CYCDUM3: 0= 0,1, or 2 cycles, 1= 3 or more cycles.

These dummy variables allow comparison of cyclers versus non-cyclers (CYCDUM1), and would also make it possible to detect a dose-response effect if one were present. Only one cycling measure was included in each regression model submitted.

Selection of Variables for the Models: For each or the four outcomes being studied in this research, all variables found to be significantly correlated with the outcome in the whole population or any subgroup of the population were included in the models for that outcome. To eliminate the possibility of multicollinearity obscuring the interpretation of results, no two variables which were very highly correlated with one another were both included in the same model. Each model was forced to include baseline measurements for the outcome variable being examined, net weight change, and the one cycling variable being evaluated in that model. Tables 27 - 30 specify which variables were submitted in each model.

Net Weight Change Groups: The regression models developed for each of the four outcomes of the research (change in cholesterol, HDL, ratio of total cholesterol to HDL, and blood pressure) were run for the whole non-excluded population and then repeated for each net weight change group within that population.

Summary of Regression Models: In summary, a total of 16 different regression models was submitted for each outcome, as illustrated in Figure 2. Each of the 16 models for each outcome included exactly the same independent variables, with the exception of the measure of weight cycling.

Weight Cycling Variable	All Non-excluded	Weight Loss Group	No Weight Change Group	Weight Gain Group
0 Cycles vs. 1,2,3+ Cycles	Model 1	Model 5	Model 9	Model 13
0-1 Cycle vs. 2-3+ Cycles	Model 2	Model 6	Model 10	Model 14
0,1,2 Cycles vs. 3+ Cycles	Model 3	Model 7	Model 11	Model 15
SEE	Model 4	Model 8	Model 12	Model 16

Figure 2 - Summary of the Sixteen Different Regression Models Submitted for Each of the Four Outcomes of the Research

RESULTS

Compared with non-cyclers, men with weight cycles did not experience smaller improvements in either total cholesterol, HDL, the ratio of total cholesterol to HDL or blood pressure, whether weight cycling was expressed in terms of number of cycles, SEE or number / size of cycles. The lack of association of weight cycling measures with CVD risk factors was observed whether individuals gained weight, lost weight or experienced minimal weight change.

Characteristics of the Study Population

Baseline Characteristics: Table 6 shows baseline characteristics of the MRFIT SI population. The study population was middle-aged (mean age 46.5), overweight (mean baseline weight 189 pounds), with elevated risk of heart disease reflected by high total cholesterol concentrations (mean 259 mg/dl), low HDL concentrations (mean 42.9 mg/dl), high ratios of total cholesterol to HDL (mean 6.08), and elevated diastolic blood pressure (mean 91.1mm Hg). The net weight change groups were not uniform with respect to baseline characteristics. The group which subsequently went on to lose at least 5% of baseline weight was older, heavier, and at higher risk in terms of total cholesterol concentration, ratio of total cholesterol to HDL and diastolic blood pressure than other groups.

Table 6 - Baseline Characteristics, All Non-excluded Subjects and by Net Weight Change Groups, MRFIT SI Group

Variables	All Non-Excluded (n=4,302) Mean (s.d.)	Weight Loss (n=1,056) Mean (s.d.)	No Weight Change (n=2,446) Mean (s.d.)	Weight Gain (n=800) Mean (s.d.)
Baseline Age	46.5 (5.8)	47.1 (5.9)[1]	46.6 (5.8)[1]	45 3 6 (5.7)[1]
Baseline Total Cholesterol, mg/dl	259 (36.6)	263 (34.9)[1]	258 (36.7)[1]	254 (37.8)[1]
Baseline HDL, mg/dl	42.9 (42.9)	42.7 (11.6)	42.8 (11.7)	43.3 (11.9)
Baseline Ratio of Total Cholesterol to HDL	6.08 (1.8)	6.2 (1.8)[1]	6.1 (1.8)	5.9 (1.8)[1]
Baseline Blood Pressure, mm Hg	91.1 (8.8)	92.4 (8.5)[1]	91.1 (8.7)[1]	89.6 (9.1)[1]
Baseline Relative Weight	1.26 (.15)	1.3 (.15)[1,2]	1.25 (.15)[1]	1.24 (.16)[2]
Baseline Weight, lb	189 (26.8)	195 (26.7)[1,2]	188 (26.1)[1]	186 (27.5)[2]
Baseline BMI, kg/m^2	27.8 (3.4)	28.5 (3.3)[1,2]	27.5 (3.2)[1]	27.3 (3.7)[2]

Note. Values in the same row with the same superscripts are significantly different from one another

Weight Cycling Patterns: Patterns of weight cycling in the SI group are summarized in Tables 7 and 8. In the entire SI group, 20% of subjects were non-cyclers, 53% experienced one cycle, 22% experienced two cycles, and 5% experienced three or more cycles over the 6-year period documented in this study. Table 7 shows the distribution of weight cycling measures by baseline BMI. The number of weight cycles was consistent across BMI groups and was similar to that in the entire population. As expected, more of the heaviest men and fewer of the leanest men fell into Tertile 3 of SEE.

Table 8 shows that the net weight change groups were also very similar to one another and to the entire population with respect to number of weight cycles,

with the exception that there were more non-cyclers in the weight gain group. The patterns of distribution of subjects by tertile of SEE was similar to that in the whole population with the exceptions that there were fewer non-cyclers in the weight loss group and more non-cyclers in the weight gain group.

Table 7 - Weight Cycling Measures in All Non-excluded Subjects and by BMI Tertile, MRFIT SI Group

Measure of Weight Cycling	All Non-excluded n (%)	BMI <26.1 n (%)	26.1<BMI<28.7 n (%)	BMI>28.7 n (%)
Number of Cycles				
0	848 (20)	293 (21)	310 (22)	245 (17)
1	2298 (53)	731 (53)	775 (54)	792 (54)
2	941 (22)	296 (21)	292 (20)	353 (24)
3+	215 (5)	63 (5)	61 (4)	91 (6)
Tertile of SEE				
Tertile 1: 1.4-3.8 lb	1422 (33)	689 (50)	543 (37)	199 (13)
Tertile 2: 3.9-5.3 lb	1413 (33)	453 (33)	507 (35)	453 (31)
Tertile 3: 5.4-20 lb	1467 (34)	241 (17)	397 (28)	829 (56)

Table 8 - Weight Cycling Measures in All Non-excluded Subjects and by Net Weight Change Group, MRFIT SI Group

Measure of Weight Cycling	All Non-excluded n (%)	Weight Loss Group n (%)	No Change Group n (%)	Weight Gain Group n (%)
Number of Cycles				
0	848 (20)	226 (21)	411 (17)	211 (26)
1	2298 (53)	541 (51)	1368 (56)	389 (49)
2	941 (22)	233 (22)	534 (22)	174 (22)
3+	215 (5)	56 (5)	133 (5)	26 (3)
Tertile of SEE				
Tertile 1: 1.4-3.8 lb	1422 (33)	235 (22)	835 (34)	313 (39)
Tertile 2: 3.9-5.3 lb	1413 (33)	367 (34)	832 (34)	239 (30)
Tertile 3: 5.4-20 lb	1467 (34)	454 (43)	779 (32)	248 (31)

Outcomes: Most members of the SI group experienced improvements in CVD risk factors by the year 6 annual visit, presumably because of the intensive interventions on those risk factors that occurred while they participated in the MRFIT. Whereas the net weight change groups were similar to one another with respect to weight cycling patterns, they were very different from one another with respect to the outcomes of the study. As expected, those who lost weight showed the greatest improvements in CVD risk factors, those who gained weight showed the smallest improvements, and those whose weight changed minimally showed an intermediate improvement. Table 9 shows mean outcomes for each weight change group. Each net weight change group was found to be significantly different from all others with respect to all outcome variables.

Table 9 - Outcomes, All Non-excluded Subjects and by Net Weight Change Groups, MRFIT SI Group

Outcomes (Year 6 - Baseline Values)	All Non-Excluded (n=4,302) Mean (s.d.)	Weight Loss (n=1,056) Mean (s.d.)	No Weight Change (n=2,446) Mean (s.d.)	Weight Gain (n=800) Mean (s.d.)
Change in Total Cholesterol, mg/dl	-23.2 (33.8)	-32.5[1] (34.8)	-22.1[1] (32.0)	-14.8[1] (35.1)
Change in HDL, mg/dl	-1.2 (9.7)	+1.5[1] (11.1)	-1.6[1] (8.7)	-3.6[1] (9.8)
Change in Ratio of Total Cholesterol to HDL	-.21 (1.6)	-.77[1] (1.8)	-.14[1] (1.5)	+.34[1] (1.7)
Change in Blood Pressure, mm Hg	-11 (9.9)	-13.6[1] (9.9)	-10.8[1] (9.6)	-8.2[1] (10.3)

Note. Values in the same row with the same superscript are significantly different from one another.

Comparisons Among Net Weight Change Groups: Table 10 shows that the net weight change groups were very different from one another with respect to most of the independent variables used in ANCOVA and regression models.

Table 10 - Mean Values for Selected Characteristics, All Non-excluded Subjects and by Net Weight Change Groups, MRFIT SI Group

Variables	All Non-Excluded (n=4,302) Mean (s.d.)	Weight Loss (n=1,056) Mean (s.d.)	No Weight Change (n=2,446) Mean (s.d.)	Weight Gain (n=800) Mean (s.d.)
Net Weight Change, lb	-1.5 (13.4)	-17.7 (8.9)[1]	-.64 (5.2)[1]	17.4 (8.7)[1]
Weight Change, Final 4 Months, lb	-2.5 (6.0)	-3.9 (6.1)[1]	-2.4 (5.4)[1]	-.7 (6.9)[1]
Weight Change, Final 12 Months, %	0.6 (3.9)	-.92 (4.2)[1]	.69 (3.3)[1]	2.5 (4.6)[1]
SEE	5.1 (2.2)	5.8 (2.7)[1]	4.7 (2.0)[1]	5.3 (2.1)[1]
Alcohol Intake, g/day	19 (25)	18 (25)[1]	19 (25)[2]	22 (26)[1,2]
Caffeine Intake, mg/day	552 (407)	528 (385)[1]	548 (400)[2]	596 (449)[1,2]
Calcium Intake, mg/day	628 (307)	644 (299)	618 (307)	635 (318)
Cholesterol Intake, mg/day	243 (138)	224 (129.9)[1]	243 (133)[1]	269 (159)[1]
% Calories from Fat	34 (7)	34 (7.1)[1]	34 (7.0)	35 (7.0)[1]
Water-soluble Fiber, gm/day	5 (2)	5 (2)[1]	5 (2.4)[1]	4 (2.3)[1]
Iron Intake, mg/day	14 (5)	14 (5)	14 (5)	14 (4.5)
P:S Ratio	1.1 (.6)	1.2 (.7)[1]	1.1 (.6)[1]	.9 (.5)[1]
Sodium Intake, mg/day	2797 (1138)	2795 (1121)	2780 (1116)	2853 (1223)
Vitamin E Intake, mg/day	10 (5.3)	11 (5.6)[1,2]	10 (5.3)[2]	9 (4.5)[1]
Exercise Duration, Baseline, min	6.8 (1.6)	6.7(1.7)[1]	6.9 (1.7)[1]	6.9 (1.6)
Exercise Opinion Year 6 (1=less, 5=more)	3.2 (1.0)	3.4 (1.0)[1]	3.2 (1)[1]	2.9 (1)[1]
Heavy LTPA, min/day	34 (72.1)	33 (84.8)	36 (72.2)	29 (49.6)
Total LTPA, min/day	105 (120.3)	105 (136.2)	108 (119.1)	97 (99.7)
Cigarettes /day, Mean Over Trial	14 (15)	10 (14)[1]	13 (15)[1]	21 (16.4)[1]

Note. Values in the same row with the same superscripts are significantly different from one another.

ANCOVA Analyses

Tables 11-30 summarize the results of the 16 primary ANCOVA models of the effect of weight cycling on each of the 4 CVD risk factors addressed in this research. In ANCOVA models, the measures of weight cycling rarely contributed significantly to the models, and in cases where they did contribute significantly, no dose-response relationship was observed between the degree of weight cycling and the degree of improvement in risk factors. Additional controls for smoking status, exercise, use of cholesterol-raising diuretics, use of cholesterol-lowering drugs and use of anti-hypertensive drugs did not, in any instance, alter the results of the primary models.

Table 11 - Mean Changes (and 95% Confidence Intervals) in Total Cholesterol by Cycling Status, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**Non-Cycler**	**Cycler**
All Non-excluded (n=4,096) Adjusted for *net wt. change group*, race, *baseline cholesterol*, P:S ratio, cigarettes/day	-21.8 (-23.9 to -19.7)	-23.5 (-24.7 to -22.3)
Weight Loss (n=961) Adjusted for: race, *baseline cholesterol, net wt. change, baseline wt., calcium intake*, cholesterol intake, *water-soluble fiber intake*, iron intake, P:S ratio, vitamin E intake, *total minutes of leisure time physical activity*, cigarettes/day	-32.7 (-36.8 to -28.6)	-32.6 (-34.7 to -30.5)
No Weight Change (n=2,123) Adjusted for: race, *age, baseline cholesterol, net wt. change, final 4-month wt. change*, cholesterol intake, P:S ratio, vitamin E intake, cigarettes/day	-19.5 (-20.5 to -18.5)	-22.7 (-24 to -21.4)
Weight Gain(n=763) Adjusted for race, *age, baseline cholesterol, relative wt. at baseline, water-soluble fiber intake*, P:S ratio, exercise duration, cigarettes/day	-14.8 (-19.3 to -10.3)	-14.7 (-17.3 to -12.1)

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 12 - Mean Changes (and 95% Confidence Intervals) in Total Cholesterol by Number of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**0 Cycles**	**1 Cycle**	**2 Cycles**	**3+ Cycles**
All Non-excluded (n=4,096) Adjusted for *net wt. change group*, race, *baseline cholesterol*, P:S ratio, cigarettes/day	-21.8 [1] (-23.9 to -19.7)	-23.1 [2] (-24.5 to -21.7)	-23.4 [3] (-25.4 to -21.4)	-29.4 [1,2,3] (-33.5 to -25.3)
Weight Loss (n=985) Adjusted for: race, *baseline cholesterol, net wt. change, baseline wt., calcium intake*, cholesterol intake, *water-soluble fiber intake*, iron intake, P:S ratio, vitamin E intake, *total minutes of leisure time physical activity*, cigarettes/day	-32.7 (-36.8 to -28.6)	-32.5 (-35 to -30)	-33.3 (-37.3 to -29.3)	-31.2 (-39.4 to -23)
No Weight Change (n=2,184) Adjusted for: race, *age, baseline cholesterol, net wt. change, final 4-month wt. change*, cholesterol intake, P:S ratio, vitamin E intake, cigarettes/day	-19.5 [1] (-22.5 to -16.5)	-22.1 [2] (-23.7 to -20.5)	-22.4 [3] (-25 to -19.8)	-31.2 [1,2,3] (-36.4 to -26)
Weight Gain (n=763) Adjusted for race, *age, baseline cholesterol, relative wt. at baseline, water-soluble fiber intake*, P:S ratio, exercise duration, cigarettes/day	-14.8 (-19.3 to -10.3)	-15.4 (-18.7 to -12.1)	-13.2 (-18.1 to -8.3)	-13.8 (-26.4 to -1.2)

Note. Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 13 - Mean Changes (and 95% Confidence Intervals) in Total Cholesterol by Tertile of SEE, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**SEE Tertile 1**	**SEE Tertile 2**	**SEE Tertile 3**
All Non-excluded (n=4,096) Adjusted for *net wt. change group*, race, *baseline cholesterol*, P:S ratio, cigarettes/day	-21.3 [1] (-23.1 to -19.5)	-23.5 (-25.1 to -21.9)	-24.4 [1] (-26 to -22.8)
Weight Loss (n=985) Adjusted for: race, *baseline cholesterol, net wt. change, baseline wt., calcium intake*, cholesterol intake, *water-soluble fiber intake*, iron intake, P:S ratio, vitamin E intake, *total minutes of leisure time physical activity*, cigarettes/day	-29.8 (-34.1 to -25.5)	-34.2 (-37.6 to -30.8)	-32.9 (-35.9 to -29.9)
No Weight Change (n=2,184) Adjusted for: race, *age, baseline cholesterol, net wt. change, final 4-month wt. change*, cholesterol intake, P:S ratio, vitamin E intake, cigarettes/day	-20.6 [1] (-22.5 to -18.7)	-22.2 (-24.3 to -20.1)	-24.4 [1] (-26.7 to -22.1)
Weight Gain (n=763) Adjusted for race, *age, baseline cholesterol, relative wt. at baseline, water-soluble fiber intake*, P:S ratio, exercise duration, cigarettes/day	-16.7 (-21.4 to -12)	-14.3 (-18.1 to -10.5)	-13.9 (-17.6 to -10.2)

Note: Values in the same row with the same superscripts are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 14 - Mean Changes (and 95% Confidence Intervals) in Total Cholesterol by Number and Size[a] of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [b]	0 Cycle	1 Small Cycle	1 Large Cycle	2 Small Cycles	2 Large Cycles	3+ Cycles
All Non-excluded (n=4,096) Adjusted for *net wt. change group*, race, *baseline cholesterol*, P:S ratio, cigarettes/day	-21.8 [1,2] (-23.9 to -19.7)	-21.5 [3,4] (-23.4 to -19.6)	-24.6 [1,3,5] (-26.4 to -22.8)	-24.7 (-27.6 to -21.8)	-22.1 [6] (-24.9 to -19.3)	-29.3 [2,4,5,6] (-33.4 to -25.2)
Weight Loss (n=985) Adjusted for: race, *baseline cholesterol, net wt. change, baseline wt., calcium intake*, cholesterol intake, *water-soluble fiber intake*, iron intake, P:S ratio, vitamin E intake, *total minutes of leisure time physical activity*, cigarettes/day	-32.6 (-36.7 to -28.5)	-29.5 (-34.1 to -24.9)	-34.2 (-37.6 to -30.8)	-34.3 (-41 to -27.6)	-32.7 (-37.7 to -27.7)	-31.3 (-39.5 to -23.1)
No Weight Change (n=2,184) Adjusted for: race, *age, baseline cholesterol, net wt. change, final 4-month wt. change*, cholesterol intake, P:S ratio, vitamin E intake, cigarettes/day	-19.4 [1] (-22.4 to -16.4)	-20.6 [2] (-22.7 to -18.5)	-24.0 [1,2] (-26.5 to -21.5)	-22.9 [3] -26.3 to -19.5)	-21.8 [4] (-25.8 to -17.8)	-31.2 [1,2,3,4] (-36.4 to -26)
Weight Gain(n=763) Adjusted for race, *age, baseline cholesterol, relative wt. at baseline, water-soluble fiber intake*, P:S ratio, exercise duration, cigarettes/day	-14.8 (-19.3 to -10.3)	-16.4 (-21.8 to -11)	-14.9 (-19.1 to -10.7)	-17.2 (-24.9 to -9.5)	-10.5 (-16.9 to -4.1)	-13.7 (-26.3 to -1.1)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Size of Cycle is defined as small if the SEE is < 4.5 pounds, and large if the SEE is ≥4.5 pounds.

[b] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 15 - Mean Changes (and 95% Confidence Intervals) in HDL by Cycling Status, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**Non-Cyclers**	**Cyclers**
All Non-excluded (n=4,243) Adjusted for net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day	[b]	[b]
Weight Loss (n=1,046) Adjusted for *age, baseline HDL, net wt. change, alcohol intake,* caffeine intake, cigarettes/day	1.7 (.3 to 3.1)	1.4 (0.7 to 2.1)
No Weight Change (n=2,249) Adjusted for: *baseline plasma cholesterol, baseline HDL, net wt. change, final 4-month wt. change, alcohol intake, caffeine intake, per cent of calories from fat,* vitamin E intake, cigarettes/day	-1 (-1.8 to -.2)	-1.8 (-2.2 to -1.4)
Weight Gain(n=787) Adjusted for: *baseline plasma cholesterol, baseline HDL,* alcohol intake, caffeine intake, cholesterol intake, per cent of calories from fat, *cigarettes/day*	-4.4 (-5.6 to -3.2)	-3.3 (-4 to -2.6)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[b] Adjusted means were not calculated because the interaction between number of cycles and net wt. change group was statistically significant.

Table 16 - Mean Changes (and 95% Confidence Intervals) in HDL by Number of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	0 Cycles	1 Cycle	2 Cycles	3+ Cycles
All Non-excluded (n=4,096) Adjusted for net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day	[b]	[b]	[b]	[b]
Weight Loss (n=1,046) Adjusted for age, *baseline HDL, net wt. change, alcohol intake,* caffeine intake, cigarettes/day	1.8 (0.4 to 3.2)	0.93 [1] (0 to 1.8)	1.8 (0.5 to 3.1)	4.6 [1] (1.9 to 7.3)
No Weight Change (n=2,249) Adjusted for: *baseline plasma cholesterol, baseline HDL, net wt. change, final 4-month wt. change, alcohol intake, caffeine intake, per cent of calories from fat,* vitamin E intake, cigarettes/day	-1.1 [1] (-1.9 to -.3)	-1.7 (-2.1 to -1.3)	-2.3 [1] (-3 to -1.6)	-1.8 (-3.2 to -.4)
Weight Gain(n=787) Adjusted for: *baseline plasma cholesterol, baseline HDL,* alcohol intake, caffeine intake, cholesterol intake, per cent of calories from fat, *cigarettes/day*	-4.4 (-5.5 to -3.2)	-3.4 (-4.2 to -2.6)	-3.3 (-4.6 to -2)	-1.0 (-4.3 to 2.2)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[b] Adjusted means were not calculated because the interaction between number of cycles and net wt. change group was statistically significant.

Table 17 - Mean Changes (and 95% Confidence Intervals) in HDL by Tertile of SEE, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**SEE Tertile 1**	**SEE Tertile 2**	**SEE Tertile 3**
All Non-excluded (n=4,243) Adjusted for *net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day*	-1 (-1.5 to -.5)	-1.4 (-1.9 to -.9)	-1.3 (-1.8 to -.8)
Weight Loss (n=1,046) Adjusted for age, *baseline HDL, net wt. change, alcohol intake,* caffeine intake, cigarettes/day	1.9 (0.5 to 3.3)	1.2 (0.1 to 2.3)	1.6 (0.6 to 2.6)
No Weight Change (n=2,249) Adjusted for: *baseline plasma cholesterol, baseline HDL, net wt. change, final 4-month wt. change, alcohol intake, caffeine intake, per cent of calories from fat,* vitamin E intake, cigarettes/day	-1.3 [1] (-1.8 to -0.8)	-2.1 [1] (-2.7 to -1.5)	-1.8 (-2.4 to -1.2)
Weight Gain(n=787) Adjusted for: *baseline plasma cholesterol, baseline HDL,* alcohol intake, caffeine intake, cholesterol intake, per cent of calories from fat, *cigarettes/day*	-4.1 (-5.3 to -2.9)	-2.6 [1] (-3.6 to -1.6)	-4.1 [1] (-5 to -3.2)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 18 - Mean Changes (and 95% Confidence Intervals) in HDL by Number and Size [a] of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models[b]	0 Cycle	1 Small Cycle	1 Large Cycle	2 Small Cycles	2 Large Cycles	3+ Cycles
All Non-excluded (n=4,243) Adjusted for net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day	[c]	[c]	[c]	[c]	[c]	[c]
Weight Loss (n=1,046) Adjusted for age, *baseline HDL, net wt. change, alcohol intake,* caffeine intake, cigarettes/day	1.7 [1] (0.3 to 3.1)	1.5 [2] (0 to 3.0)	0.6 [3] (-.5 to 1.7)	1.8 (-.4 to 4.0)	1.9 (0.2 to 3.6)	4.7 [1,2,3] (2.0 to 7.4)
No Weight Change (n=2,249) Adjusted for: *baseline plasma cholesterol, baseline HDL, net wt. change, final 4-month wt. change, alcohol intake, caffeine intake, per cent of calories from fat,* vitamin E intake, cigarettes/day	-1.0 [1] (-1.8 to -0.2)	-1.5 [2] (-2.1 to -.09)	-1.9 (-2.6 to -1.2)	-2.0 (-2.9 to -1.1)	-2.6 [1,2] (-3.7 to -1.5)	-1.6 (-3 to -.2)
Weight Gain(n=787) Adjusted for: *baseline plasma cholesterol, baseline HDL,* alcohol intake, caffeine intake, cholesterol intake, per cent of calories from fat, *cigarettes/day*	-4.4 [1] (-5.6 to -3.2)	-3.7 (-5.1 to -2.3)	-3.2 (-4.3 to -2.1)	-1.8 [1] (-3.8 to .02)	-4.4 (-6.0 to -2.8)	-1.0 (-4.3 to 2.3)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Size of cycle is defined as small if the SEE is < 4.5 pounds, and large if the SEE is ≥4.5 pounds.

[b] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[c] Adjusted means were not calculated because the interaction between number of cycles and net wt. change group was statistically significant.

Table 19 - Mean Changes (and 95% Confidence Intervals) in the Ratio of Total Cholesterol to HDL by Cycling Status, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**Non-Cyclers**	**Cyclers**
All Non-excluded (n=4,243) Adjusted for *net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day*	-.18 (-.28 to -.08)	-.19 (-.25 to -.13)
Weight Loss (n=1,046) Adjusted for *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake,* caffeine intake, *calcium intake*, iron intake, sodium intake, vitamin E intake, cigarettes/day	-.8 (-1 to -.6)	-.8 (-.9 to -.7)
No Weight Change (n=2,410) Adjusted for: *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake, caffeine intake,* cigarettes/day	-.20 (-.34 to -.06)	-0.13 (-.19 to -.07)
Weight Gain(n=787) Adjusted for: *baseline ratio of total cholesterol to HDL,* caffeine intake, *cholesterol intake, cigarettes/day*	.45 (.23 to .67)	.30 (.16 to .44)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 20 - Mean Changes (and 95% Confidence Intervals) in the Ratio of Total Cholesterol to HDL by Number of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**0 Cycles**	**1 Cycle**	**2 Cycles**	**3+ Cycles**
All Non-excluded (n=4,243) Adjusted for *net wt. change group, baseline HDL, baseline plasma cholesterol caffeine intake, alcohol intake, cigarettes/day*	-.18 (-.28 to -.08)	-.19 (-.25 to -.13)	-.15 (-.25 to -.05)	-.37 (-.57 to -.17)
Weight Loss (n=1,046) Adjusted for *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake,* caffeine intake, *calcium intake*, iron intake, sodium intake, vitamin E intake, cigarettes/day	-.8 (-1.0 to -0.6)	-.7 (-.82 to -.58)	-.8 (.1.0 to -.6)	-1.0 (-1.39 to -.61)
No Weight Change (n=2,410) Adjusted for: *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake, caffeine intake,* cigarettes/day	-.20 (-.34 to -.06)	-.16 (-.24 to -.08)	-.04 (-.16 to 0.08)	-.22 (-.44 to 0)
Weight Gain(n=787) Adjusted for: *baseline ratio of total cholesterol to HDL,* alcohol intake, caffeine intake, *cholesterol intake, cigarettes/day*	.45 (.23 to .67)	.30 (.14 to .46)	.37 (.13 to .61)	-.06 (-.71 to .59)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 21 - Mean Changes (and 95% Confidence Intervals) in the Ratio of Total Cholesterol to HDL by Tertile of SEE, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**SEE Tertile 1**	**SEE Tertile 2**	**SEE Tertile 3**
All Non-excluded (n=4,243) Adjusted for *net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day*	-.17 (-.25 to -.09)	-.17 (-.25 to -.09)	-.21 (-.29 to -.13)
Weight Loss (n=1,046) Adjusted for *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake,* caffeine intake, *calcium intake*, iron intake, sodium intake, vitamin E intake, cigarettes/day	-.83 (-1.03 to -.63)	-.76 (-.92 to -.6)	-.73 (-.87 to -.59)
No Weight Change (n=2,410) Adjusted for: *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake, caffeine intake,* cigarettes/day	-.18 (-.26 to -.1)	-.11 (-.21 to -.01)	-.12 (-.22 to -.02)
Weight Gain (n=787) Adjusted for: *baseline ratio of total cholesterol to HDL,* alcohol intake, caffeine intake, *cholesterol intake, cigarettes/day*	.39 (.17 to .61)	.31 (.13 to .49)	.34 (.16 to .52)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 22 - Mean Changes (and 95% Confidence Intervals) in the Ratio of Total Cholesterol to HDL by Number and Size [a] of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [b]	0 Cycle	1 Small Cycle	1 Large Cycle	2 Small Cycles	2 Large Cycles	3+ Cycles
All Non-excluded (n=4,243) Adjusted for *net wt. change group, baseline HDL, caffeine intake, alcohol intake, cigarettes/day*	-.17 (-.27 to -.07)	-.16 (-.26 to -.06)	-.22 (-.3 to -.14)	-.16 (-.3 to -.02)	-.14 (-.28 to 0)	-.36 (-.56 to -.16)
Weight Loss (n=1,046) Adjusted for *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake,* caffeine intake, *calcium intake*, iron intake, sodium intake, vitamin E intake, cigarettes/day	-.79 (-.99 to -.59)	-.84 (-1.06 to -.62)	-.63 (-.79 to -.47)	-.83 (-1.14 to -.52)	-.81 (-1.06 to -.56)	-1.0 (-1.39 to -.61)
No Weight Change (n=2,410) Adjusted for: *baseline ratio of total cholesterol to HDL, net wt. change, alcohol intake, caffeine intake,* cigarettes/day	-.20 [1] (-.34 to -.06)	-.14 [2] (-.24 to -.04)	-.18 [3] (-.28 to -.08)	-.14 [4] (-.3 to .02)	.09 [1,2,3,4,5] (-.09 to .27)	-.22 [5] (-.44 to 0)
Weight Gain(n=787) Adjusted for: *baseline ratio of total cholesterol to HDL,* alcohol intake, caffeine intake, *cholesterol intake, cigarettes/day*	.45 (.23 to .67)	.33 (.08 to .58)	.28 (.08 to .48)	.40 (.03 to .77)	.35 (.04 to .66)	-.06 (-.67 to .55)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Size of Cycle is defined as small if the SEE is < 4.5 pounds, and large if the SEE is ≥4.5 pounds.

[b] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

Table 23 - Mean Changes (and 95% Confidence Intervals) in Diastolic Blood Pressure by Cycling Status, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**Non-Cyclers**	**Cyclers**
All Non-excluded (n=4,393) Adjusted for net wt. change group, race, baseline blood pressure, age, cigarettes/day	[b]	[b]
Weight Loss (n=1,059) Adjusted for race, *baseline blood pressure, age, net wt. change,* alcohol intake, *cigarettes/day*	-13.5 (-14.5 to -12.5)	-13.6 (-14.1 to -13.1)
No Weight Change (n=2,438) Adjusted for: race, *age*, relative wt. at baseline, *baseline blood pressure,* net wt. change, *final 12-month wt. change,* caffeine intake calcium intake, cholesterol intake, iron intake, vitamin E intake, exercise duration, *cigarettes/day*	-9.6 [1] (-10.3 to-8.9)	-10.9 [1] (-11.2 to -10.6)
Weight Gain(n=799) Adjusted for: race , *age, baseline blood pressure,* caffeine intake, cholesterol intake, per cent of calories from fat, exercise duration, cigarettes/day	-8.5 (-9.4 to -7.6)	-8.0 (-8.6 to -7.4)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[b] Adjusted means were not calculated because the interaction between number of cycles and net weight change group was statistically significant.

Table 24 - Mean Changes (and 95% Confidence Intervals) in Diastolic Blood Pressure by Number of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	0 Cycles	1 Cycle	2 Cycles	3+ Cycles
All Non-excluded (n=4,393) Adjusted for net wt. change group, race, baseline blood pressure, age, cigarettes/day	[b]	[b]	[b]	[b]
Weight Loss (n=1,059) Adjusted for race, *baseline blood pressure, age, net wt. change,* alcohol intake, *cigarettes/day*	-13.5 (-14.5 to -12.5)	-13.6 (-14.2 to -13)	-14.1 (-15 to -13.2)	-12.2 (-14.2 to -10.2)
No Weight Change (n=2,438) Adjusted for: race, *quintile of total minutes of physical activity, age,* relative wt. at baseline, *baseline blood pressure,* net wt. change, *final 12-month wt. change,* caffeine intake, calcium intake, cholesterol intake, iron intake, vitamin E intake, exercise duration, *cigarettes/day*	-9.6 [1,2] (-10.3 to -8.9)	-10.8 [1] (-11.2 to -10.4)	-11.4 [2] (-12 to -10.8)	-10.3 (-11.5 to -9.1)
Weight Gain (n=745 White, 54 Black) Adjusted for: *race,*[c] *age, baseline blood pressure,* caffeine intake, cholesterol intake, per cent of calories from fat, exercise duration, cigarettes/day	White: -8.7 (-9.7 to -7.7)	White: -8.1 (-8.8 to -7.4)	White: -8.2 -9.3 to -7.1)	White: -6.6 (-9.3 to -3.9)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[b] Adjusted means were not calculated because the interaction between number of cycles and net weight change group was statistically significant.

[c] Interaction between number of cycles and race necessitated separate analysis by race; there were too few Black subjects to perform Analysis of Covariance.

Table 25 - Mean Changes (and 95% Confidence Intervals) in Diastolic Blood Pressure by Tertile of SEE, MRFIT SI Group

Population Subgroup/ Variables Included in Models [a]	**SEE Tertile 1**	**SEE Tertile 2**	**SEE Tertile 3**
All Non-excluded (n=4,393) Adjusted for net wt. change group, race, baseline blood pressure, age, cigarettes/day	[b]	[b]	[b]
Weight Loss (n=1,059) Adjusted for race, *baseline blood pressure, age, net wt. change,* alcohol intake, *cigarettes/day*	-14.1 (-15.1 to -13.1)	-13.0 (-13.8 to -12.2)	-13.8 (-14.5 to -13.1)
No Weight Change (n=2,500) Adjusted for: race, *age,* relative wt. at baseline, *baseline blood pressure,* net wt. change, *final 12-month wt. change,* caffeine intake calcium intake, cholesterol intake, iron intake, vitamin E intake, exercise duration, *cigarettes/day*	-10.5 [1] (-10.9 to -10.1)	-11.3 [1,2] (-11.8 to -10.8)	-10.5 [2] (-11 to -10)
Weight Gain(n=815) Adjusted for: race, *age, baseline blood pressure,* caffeine intake, cholesterol intake, per cent of calories from fat, exercise duration, cigarettes/day	-8.3 (-9.3 to -7.3)	-8.5 (-9.3 to -7.7)	-7.8 (-8.6 to -7)

Note: Values in the same row with the same superscript are significantly different from one another .

[a] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[b] Adjusted means were not calculated because the interaction between number of cycles and net weight change group was statistically significant.

Table 26 - Mean Changes (and 95% Confidence Intervals) in Diastolic Blood Pressure by Number and Size[a] of Cycles, MRFIT SI Group

Population Subgroup/ Variables Included in Models [b]	0 Cycle	1 Small Cycle	1 Large Cycle	2 Small Cycles	2 Large Cycles	3+ Cycles
All Non-excluded (n=4,393) Adjusted for net wt. change group, race, baseline blood pressure, age, cigarettes/day	[c]	[c]	[c]	[c]	[c]	[c]
Weight Loss (n=1,059) Adjusted for race, *baseline blood pressure, age, net wt. change,* alcohol intake, *cigarettes/day*	-13.5 (-14.5 to -12.5)	-13.6 (-14.6 to -12.6)	-13.6 (-14.4 to -12.8)	-13.9 (-15.4 to -12.4)	-14.1 (-15.3 to -12.9)	-12.2 (-14.2 to -10.2)
No Weight Change (n=2,248 White, 184 Black) Adjusted for: *race,*[d] *age,* relative wt. at baseline, *baseline blood pressure,* net wt. change, *final 12-month wt. change,* caffeine intake calcium intake, cholesterol intake, iron intake, vitamin E intake, exercise duration, *cigarettes/day*	White: -9.8 [1,2,3] (-10.5 to -9.1) Black: -9.6 [1] (-11.8 to -7.4)	White: -11.0 [1] (-11.5 to -10.5) Black: -13.4 [1] (-15.2 to -11.6)	White: -10.5 [4] (-11.1 to -9.9) Black: -10.6 (-12.8 to -8.4)	White: -11.7 [2,4] (-12.5 to -10.9) Black: -12.3 (-14.8 to -9.8)	White: -11.1 [3] (-12.1 to -10.1) Black: -11.3 (-14.2 to -8.4)	White: -10.4 (-11.7 to -9.1) Black: -9.5 (-13.4 to -5.6)
Weight Gain (n=815) Adjusted for: race, *age, baseline blood pressure,* caffeine intake, cholesterol intake, per cent of calories from fat, exercise duration, cigarettes/day	-8.5 (-9.4 to -7.6)	-8.0 (-9.1 to -6.9)	-8.0 (-8.9 to -7.1)	-9.1 (-10.7 to -7.5)	-7.7 (-9.1 to -6.3)	-6.7 (-9.2 to -4.2)

Note: Values in the same row with the same superscript are significantly different from one another.

[a] Size of Cycle is defined as small if the SEE is < 4.5 pounds and large if the SEE is ≥4.5 pounds.

[b] Variables listed were submitted in the original ANCOVA model. Those in italics were found to contribute significantly to the model and were retained for the final model in which adjusted means were calculated .

[c] Adjusted means were not calculated because the interaction between number of cycles and net weight change group was statistically significant.

[d] Interaction between wt. cycling and race necessitated separate analysis by race.

Regression Analyses

Tables 27-30 summarize the results of regression analyses. In no regression model was the degree of weight cycling inversely associated with improvements in CVD risk factors, as was hypothesized. The partial regression coefficient for the weight cycling measure was not significantly different from 0 in 53 of the 64 models. In the 11 instances where the partial regression coefficient was statistically different from 0, it generally reflected small improvements in risk factors associated with cycling which were not clinically significant. For example, in blood pressure regression Model 1, the partial regression coefficient for Dummy Variable 1 (where 0 = no cycles and 1=1, 2, or 3+ cycles) was -.56. This is interpreted to mean that having 1 or more cycles is associated with a reduction in blood pressure that is 0.56 mm Hg lower than the reduction associated with no cycles.

Table 27 - Partial Regression Coefficients (and 95% Confidence Intervals) for Measures of Weight Cycling from Regression Models for Total Cholesterol, MRFIT SI Group

Weight Cycling Variable	All Non-excluded [a] (n=3,535)	Weight Loss Group (n=875)	No Weight Change Group (n=2,010)	Weight Gain Group (n=650)
0 Cycles vs. 1,2,3+ Cycles	-1.04 (-3.55 to 1.55)	-0.5 (-5.4 to 4.4)	-3.5 [b] (-6.83 to -.17)	.32 (-5.36 to 6)
0-1 Cycle vs. 2-3+ Cycles	-1.7 (-3.86 to .46)	-0.7 (-5.21 to 3.81)	-2.3 (-5.04 to .44)	0.5 (-5.18 to 6.18)
0-2 Cycles vs. 3+ Cycles	-6.2 [b] (-10.8 to -1.79)	0.3 (-8.52 to 9.12)	-9.8 [b] (-15.3 to -4.31)	3.1 (-12.19 to 18.4)
SEE	-0.7 [b] (-1.09 to -.31)	-0.1 (-1.08 to .88)	-0.8 [b] (-1.39 to -.21)	-0.7 (-1.88 to .48)

Note. Stepwise multiple regression models submitted included age, race (dummy variable), baseline cholesterol, net weight change, weight change in the final 4-month interval, relative weight at baseline, use of lipid-raising diuretics (dummy variable), having a condition or medication affecting weight (dummy variable), exercise duration at baseline, average total minutes per day of LTPA, mean number of cigarettes per day and mean intake over years 1-3 of calcium, cholesterol, water-soluble fiber, iron, P:S ratio and vitamin E.

[a] Excluded: Subjects missing 4 or more weight measurements and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

[b] Significantly different from 0

Table 28 - Partial Regression Coefficients (and 95% Confidence Intervals) for Measures of Weight Cycling from Regression Models for HDL, MRFIT SI Group

Weight Cycling Variable	All Non-excluded[a] (n=4,136)	Weight Loss Group (n=1,019)	No Weight Change Group (n=2,344)	Weight Gain Group (n=773)
0 Cycles vs. 1,2,3+ Cycles	-0.20 (-.87 to .47)	-0.08 -1.63 to 1.47)	-0.53 (-1.39 to .33)	0.92 (-.43 to 2.27)
0-1 Cycle vs. 2-3+ Cycles	0.09 -.52 to .7)	1.3 (-.11 to 2.71)	-0.62 (-1.35 to .11)	0.88 (-.49 to 2.25)
0-2 Cycles vs. 3+ Cycles	0.87 (-.35 to 2.09)	3.4 [b] (.66 to 6.14)	-0.52 (-1.93 to .89)	3.01 (-.32 to 6.34)
SEE	0.16 [b] (.02 to .3)	.09 (-.09 to .27)	.05 (-.13 to .23)	.26 (-.05 to .57)

Note. Stepwise multiple regression models submitted included race (dummy variable), baseline HDL, net weight change, weight at baseline, use of lipid-raising diuretics (dummy variable), having a condition or medication affecting weight (dummy variable), mean number of cigarettes per day and mean intake over years 1-3 of alcohol, caffeine, cholesterol, vitamin E, and per cent of calories as fat.

[a] Excluded: Subjects missing 4 or more weight measurements and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

[b] Significantly different from 0

Table 29 - Partial Regression Coefficients (and 95% Confidence Intervals) for Measures of Weight Cycling from Regression Models for the Ratio of Total Cholesterol to HDL, MRFIT SI Group

Weight Cycling Variable	All Non-excluded [a] (n=3,655)	Weight Loss Group (n=918)	No Weight Change Group (n=2,065)	Weight Gain Group (n=672)
0 Cycles vs. 1,2,3+ Cycles	0.03 (-.09 to .15)	-0.07 (-.32 to .18)	0.05 (-.11 to .21)	-0.04 (-.31 to .23)
0-1 Cycle vs. 2-3+ Cycles	0.02 (-.1 to .14)	-0.12 (-.36 to .12)	0.09 (-.05 to .23)	0.002 (-.27 to .28)
0-2 Cycles vs. 3+ Cycles	-0.15 (-.37 to .07)	-0.28 (-.73 to .17)	-.03 (-.28 to .22)	-0.33 (-1 to .34)
SEE	-0.03 [b] (-.05 to -.01)	-0.01 (-.07 to .05)	-0.003 -.04 to .04)	-0.06 (-.12 to 0)

Note. Stepwise multiple regression models submitted included age, race (dummy variable), baseline plasma cholesterol, baseline HDL, net weight change, weight change in the final 4-month interval, weight at baseline, use of lipid-raising diuretics (dummy variable), having a condition or medication affecting weight (dummy variable), exercise duration at baseline, average total minutes per day of LTPA, mean number of cigarettes per day and mean intake over years 1-3 of caffeine, calcium, cholesterol, sodium, water-soluble fiber, iron, P:S ratio and vitamin E.

[a] Excluded: Subjects missing 4 or more weight measurements and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

[b] Significantly different from 0

Table 30 - Partial Regression Coefficients (and 95% Confidence Intervals) for Measures of Weight Cycling from Regression Models for Blood Pressure, MRFIT SI Group

Weight Cycling Measure	All Non-excluded [a] (n=4,405)	Weight Loss Group (n=985)	No Weight Change Group (n=2,299)	Weight Gain Group (n=761)
0 Cycles vs. 1,2,3+ Cycles	-0.6 [b] (-1.19 to -.01)	-0.4 (-1.58 to 0.78)	-1.3 [b] (-2.6 to -.54)	0.4 (-.76 to 1.56)
0-1 Cycle vs. 2-3+ Cycles	-0.3 (-.89 to .29)	-0.5 (-1.48 to 0.48)	-0.4 (-1.05 to .25)	0.10 (-1.12 to 1.32)
0-2 Cycles vs. 3+ Cycles	0.9 (-.08 to 1.88)	1.8 (-.28 to 3.88)	0.7 (-.55 to 1.95)	1.3 (-1.44 to 4.04)
SEE	-0.09 (-.21 to .03)	-0.30 [b] (-.52 to -.08)	-0.01 (-.17 to 0.15)	0.12 (-.13 to .37)

Note. Stepwise multiple regression models submitted included age, race (dummy variable), baseline blood pressure, net weight change, weight change in the final 12-month interval, relative weight at baseline, use of antihypertensive drugs (dummy variable), having a condition or medication affecting weight (dummy variable), having a condition or medication affecting blood pressure (dummy variable), exercise duration at baseline, average total minutes per day of LTPA, mean number of cigarettes per day and mean intake over years 1-3 of calcium, cholesterol, water-soluble fiber, iron, P:S ratio and vitamin E, alcohol, caffeine and per cent of calories as fat.

[a] Excluded: Subjects missing 4 or more weight measurements, and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, renal disease, angina, primary aldosteronism and Cushing's disease.

[b] Significantly different from 0.

Preliminary ANOVA on Homogeneous Groups

When the effects of baseline weight and net weight change were essentially removed by restriction of the population to small groups of men homogeneous with respect to these two characteristics, weight cycling did not predict changes in total cholesterol or changes in blood pressure, whether weight cycling was quantified by number of cycles, cycling status (non-cycler vs.

cycler) or tertile of SEE. Table 31 shows the adjusted mean outcomes by cycling status only. The differences between cyclers and non-cyclers in mean changes in cholesterol and blood pressure were not statistically significant.

Table 31 - Adjusted[a] Mean Changes (and 95% Confidence Intervals) in Total Cholesterol and Blood Pressure, Homogeneous Weight Groups, MRFIT SI Group

Outcome	Non-cyclers	Cyclers
Change in Total Cholesterol, mg/dl (Year 6 - Baseline)	-19.2 (-31.3 to -7.1) (n=28)	-25.6 (-31.6 to -19.6) (n=115)
Change in Blood Pressure, mm Hg (Year 6 - Baseline)	-10.3 (-13.8 to -6.8) (n=29)	-10.6 (-12.3 to -8.9) (n=127)

[a] Adjusted for net weight change groups

Effects of Dropping Year 7 Measurements

Table 32 shows that those who were present for their year 7 physical exam were not significantly different from those who were absent in terms of age, baseline weight, relative weight at baseline, baseline total cholesterol or net change in total cholesterol as of year 6. However, those who were present at year 7 had lower baseline blood pressure, showed less improvement in blood pressure by year 6 and had lost considerably more weight by year 6 than those who were absent at year 7.

Comparisons of Subjects Dropped from Analysis from Those Retained

Subjects dropped from analysis due to missing weight data were very similar to those with "enough" data with respect to baseline characteristics.

However, as expected with less compliant subjects, they showed poorer weight loss and smaller improvements in cholesterol and blood pressure than those with "enough" data (See Table 33).

T-tests comparing the SI and UC Groups showed that the two groups were not significantly different with respect to these baseline characteristics: age, weight, relative weight, blood pressure, total cholesterol, HDL or low density lipoproteins (See Table 34).

Table 32 - Comparison of Subjects Present at Year 7 Annual Exam with Those Absent, Selected Variables, MRFIT Population

Variables	Present Year 7 (n=5215) Mean (s.d.)	Absent Year 7 (n=6090) Mean (s.d.)
Baseline Age, yr	46.3 (5.9)	46.19 (5.9)
Baseline Weight, lb	189.1 (27.1)	188.9 (28.6)
Relative Weight at Baseline	1.26 (1.6)	1.26 (1.6)
Baseline Diastolic Blood Pressure, mm Hg	90.3 [1] (8.8)	91.0 [1] (8.6)
Baseline Total Cholesterol, mg/dl	257.1 (35.5)	258.1 (38.3)
Change in Blood Pressure (Year 6 - Baseline), mm Hg	-8.4 [1] (9.9)	-8.9 [1] (10.3)
Change in Total Cholesterol (Year 6 - Baseline), mg/dl	-19.8 (32.6)	-19.8 (33.6)
Weight Change (Year 6 - Baseline), lb	-8.0 [1] (13.2)	+6.9 [1] (13.7)

Note. Values in the same row with the same superscript are significantly different from one another.

Table 33 - Comparison of Subjects Dropped from Analysis Because of Missing Weight Data with Those Who Had "Enough" Data, MRFIT SI Group

Parameters Compared	Dropped [a] (n=1,496) Mean (s.d.)	Retained (n=4,932) Mean (s.d.)
Baseline Age, yr	45 [1] (5.8)	47 [1] (6.2)
Baseline Weight, lb	190.2 (28.4)	189.0 (27.1)
Baseline Relative Weight	1.27 (1.7)	1.26 (1.5)
Baseline Total Cholesterol, mg/dl	256.9 (37.4)	258.1 (36.7)
Baseline Blood Pressure, mm Hg	89.4 [1] (8.9)	91.1 [1] (8.7)
Baseline HDL, mg/dl	42.2 [1] (12.6)	43.1 [1] (11.8)
Net Change in Total Cholesterol, mg/dl (Year 6 - Baseline)	-17.3 [1] (31.7) (n=782)	-23.3 [1] (33.6) (n=4,698)
Net Change in Blood Pressure, mm Hg (Year 6 - Baseline)	-6.2 [1] (10.8) (n=829)	-10.9 [1] (9.9) (n=4,927)
Wt. Change in First 4 Months, lb	-.87 [1] (8.7) (n=1224)	-1.93 [1] (9.1) (n=4850)
Wt. Change in First Year, lb	-2.9 [1] (10.8) (n=1,194)	-4.1 [1] (10.5) (n=4,916)

Note. Values in the same row with the same superscripts are significantly different from one another.

[a] Dropped for missing more than three 4-month interval weights

Table 34 - Comparison of Mean Values for Selected Baseline Characteristics, MRFIT UC and SI Groups

Baseline Characteristic	Usual Care (n=6436) Mean	(s.d.)	Special Intervention (n=6422) Mean	(s.d.)
Age	46.1	(5.9)	46.29	(6.0)
Weight, lb.	189.0	(27)	189.3	(27.4)
Relative Weight	1.26	(.16)	1.26	(.16)
Blood Pressure, mm. Hg	90.7	(8.7)	90.7	(8.8)
Total Cholesterol, mg/dl	257.5	(37.5)	257.8	(36.9)
HDL, mg/dl	43.0	(11.8)	43.0	(12.0)
Low Density Lipoproteins, mg/dl	163.0	(37.0)	162.5	(36.2)

Note. There were no significant differences between groups.

DISCUSSION

This research was undertaken in response to the puzzling findings among several population groups,[2,3,4,113,116] including the MRFIT population[1] studied in this research, that weight cycling was associated with increased mortality. No credible mechanism has been identified to explain this phenomenon. This research proposes a mechanism and tests whether that mechanism was operating in the Special Intervention Group of the MRFIT population. It was hypothesized that individuals who weight cycled experienced smaller improvements in the cardiovascular risk factors total cholesterol, HDL, the ratio of total cholesterol to HDL, and blood pressure - compared with those who did not cycle.

The results of data analyses, shown in Tables 11-30, provided no support for this hypothesis. In order for the hypothesis to have been supported, a strong negative association between measures of weight cycling and improvements in risk factors would have to have been seen, as well as a dose-response relationship between the degree of weight cycling and degree of improvement in risk. Neither of these conditions was met. This lack of association between weight cycling measures and CVD risk factors is consistent with the few other

studies published to date addressing the effects of weight cycling on total cholesterol and blood pressure.[13,59]

Issue: Are the Weight Cyclers in the Present Study the Same Men Who Were Found to be at Greater Risk of Mortality?

If one is looking for a mechanism to explain increased mortality with weight cycling, the population studied should be one in which increased mortality with cycling has been documented. This was the case for the MRFIT SI Group on which this study was based. The question arises, however, of whether the exclusions deemed necessary for a study of blood lipids and blood pressure resulted in purging from the data set the individuals who died during the 2-5 year follow-up period for which mortality risks were computed by Blair et al.[1] A careful comparison of exclusions in the mortality study and the present study is warranted.

Comparison of subjects excluded for medical conditions: The only medical condition which served as a basis for exclusion in the mortality study was cancer.[1] In the present study, in addition to men with cancer, 31 men with thyroid disease were also excluded because of the drastic effects hypo- and hyperthyroidism exert on weight. It is certainly possible that the 31 SI men with thyroid disease who were excluded were among the 98 SI who died during the 2-5 year follow-up period of the mortality study, but there is no reason to believe they constituted a disproportionate share of those 98 deaths.

No other men were completely excluded from the present study because of any medical condition. In models developed for each outcome, men with

conditions drastically affecting that outcome were excluded. Leaving in those individuals would make interpretation of results impossible, in that whatever effect weight cycling may have had on the outcome would be overshadowed by the effect of that condition. However, men excluded from blood pressure analyses were not excluded from blood lipid analyses and men excluded from blood lipid analyses were not excluded from blood pressure analyses.

Comparison of subjects excluded for missing data: In the mortality study, approximately 264 men were excluded who were not alive at the seventh anniversary of their randomization, and 499 men were excluded who were missing more than 4 of their 8 annual weight measurements or missing the year 6 or year 7 weights. In the present study, 1,498 SI men missing more than 3 of their 4-month interval weights or missing their year 6 weight were excluded. The 1,498 men thus eliminated would have included most of the 264 men who died during the study and at least some of the 499 men eliminated in the mortality study. It is estimated that approximately 800 men were eliminated from the present study because of missing data who were retained in the mortality study.

The requirement, in the present study, for thorough documentation of weights was considered essential for creating a reliable and valid measure of weight cycling; however this stricter criterion may well have eliminated some of the less-compliant men who could be expected to have a higher risk of mortality.

In the mortality study,[1] 28 men with any infeasible weight measurements were dropped. In the current study, infeasible weight measurements were identified and replaced with estimated weights. This discrepancy in approach

had very minor effect on the composition of the study population, because very few individuals were found to have infeasible weights, and having an infeasible weight would not be a reflection of either greater or lesser risk of mortality.

Summary of effects of exclusions: In summary, the current study eliminated two categories of men who were included in the mortality study who may have been among those who died during the follow-up period in the MRFIT mortality study - 31 with thyroid disease and approximately 800 subjects who were missing more than 3 weights. These exclusions were considered necessary for the scientific integrity of the present study, but could have eliminated from the population some of the 98 men who died during the follow-up period.

Comparison of subjects categorized as weight cyclers: Another source of discrepancy between the study population for the present research and that of the mortality study[1] was a difference in how subjects were assigned "cycler" or "non-cycler" status. For most mortality analyses, only 4-8 weights taken at 12-month intervals were used when determining whether each subject had experienced at least one weight cycle. Because they used less than half of the available weight data to document cycling status, Blair et al. misclassified about half of the subjects who experienced at least one weight cycle as "non-cyclers." In the present study, the same definition of a weight cycle was used (loss and regain of 5% of weight), but the more complete documentation of weight in the present study allowed more precise identification of weight cycling status.

The continuous measure of weight cycling used in the mortality study was also different from that used in the present study. Standard deviation of weight was used in the mortality study, while the current study used standard error or the estimate of the regression of weight on time (SEE). SEE was used in the present research because it differentiated between weight change due to steady loss or gain and weight change from cycling, and was therefore considered a better measure of weight cycling.

It should be noted that it had been the intention of the researcher to categorize subjects in exactly the same ways they had been categorized in the mortality study by Blair et al.[1], so that the results of the present research would be directly comparable to the mortality findings. The decision to depart from this plan was made purposefully, because it was judged that the weight cycling measures used in the mortality study were too imprecise to allow testing of the hypothesis related to mechanisms.

Significance of the differences in methodology: Because of the differences in exclusions and in categorization of men by cycling status, there is no assurance that the subjects classified as weight cyclers in the present study were identical with the subjects classified as cyclers in the mortality study. Although it would have been ideal if the study populations were identical, the discrepancy does not invalidate the present study. The question being addressed in the present study is whether weight cycling had adverse effects on blood pressure and blood lipids for the MRFIT SI group. No adverse effect of weight cycling was observed for any outcome, in any subset of the population.

In fact, if any effect was found, it was a very slight positive association between degree of cycling and improvements in outcomes. There is no basis for believing that weight cycling had a completely opposite effect on the 831 subjects dropped from analysis, or that the magnitude of the opposite effect was so great that it accounted for most of the deaths observed in the mortality study by Blair et al.[1]

Implications for future research: Although the results of the present study contribute to the understanding of the effects of weight cycling on the CVD risk factors examined, it would be most worthwhile to obtain the mortality data for the population, and determine whether the same elevated risk of mortality found in weight cyclers would still be observed using the more precise definitions of weight cycling now available.

Does Weight Cycling Have Different Effects on Heavy Men than on Leaner Men?

The association Blair and co-workers found between increased mortality and weight cycling was found only in men in the lower range of the weight distribution, but was not found in the heaviest men.[1] The question of whether weight cycling could be harmful for moderately heavy men but not harmful or somehow beneficial for obese men is an important one, because heavier men are more likely to diet and are therefore much more likely to be weight cyclers. This was confirmed in the current study; Table 7 shows that the heaviest men had similar numbers of episodes of weight cycling as their leaner counterparts,

but that the magnitude of the weight variability (SEE) was greatest in the heaviest men.

In this study, when men were classified by tertile of baseline BMI, there was no significant interaction between weight cycling and baseline BMI (data not shown). In other words, the effects of weight cycling on blood pressure and cholesterol were no different for the heavier men than for the slimmer men. Greater magnitude of weight cycling was not associated with either better or worse changes in risk factors for men at any weight with one exception. That one exception, illustrated in Figure 3, was that, among the heaviest men, the 91 men having 3 or more weight cycles had a mean decrease in total cholesterol of 12% compared to decreases of only 8-9% for the 1,390 men with 0-2 weight cycles. This difference was statistically significant.

It is unlikely that this isolated instance of improvement in a risk factor associated with the most extreme weight cycling constitutes evidence that weight cycling is beneficial to heavier men for three reasons. First, there were no significant differences between men with no cycles and men with one cycle or between men with one cycle and men with two cycles. In other words, there was no dose-response relationship between degree of cycling and improvement in total cholesterol. Second, the better improvement in cholesterol for heavy men with more weight cycling was not observed when weight cycling was defined in terms of SEE. It should be noted that SEE may be a better reflection of magnitude of weight variability than is number of cycles, and that there was a greater proportion of heavier men when compared to leaner men in the highest

SEE tertile. Third, when other characteristics of the heaviest men were studied, it was seen that the mean weight change during the 4-month interval before the final cholesterol measurement was taken was a loss of 4.4 pounds, significantly greater than the weight changes among those with 0, 1, or 2 cycles (ANOVA, post hoc test Bonferroni Inequality). Such a weight loss could be responsible for small improvements in cholesterol over the final 4-month interval of the study.

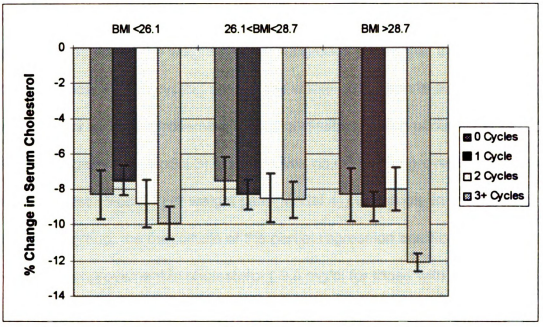

Figure 3 - Adjusted Mean Per Cent Change (and 95% Confidence Interval) in Total Cholesterol from Baseline to Year 6 , by Tertile of Baseline BMI and Number of Weight Cycles, MRFIT SI Group

Could Weight Cycling be Interpreted as Being Beneficial in Any Cases?

In the few models where significant differences were found in outcomes between men with differing numbers of cycles, it was occasionally found that having more cycles was associated with better outcomes than was having fewer cycles. It is important to raise the question of whether cycling may be beneficial in some instances. In two instances, regression models suggested that having three or more weight cycles could be associated with improvements in risk factors which were of a magnitude approaching clinical significance.

- For total cholesterol regression Model 3, based on the entire non-excluded population, the partial regression coefficient for Dummy Variable 3 was -6.3, which is interpreted to mean that having 3 or more cycles was associated with an improvement in cholesterol that was 6.3 mg/dl better than the improvement

associated with having 0, 1 or 2 cycles. Examination of the total cholesterol regression results for the weight change subgroups shows that the improvement in total cholesterol with cycling seen in the whole population is actually accounted for by the improvement in total cholesterol which occurred in the no weight change group (Model 3), as there was no relative improvement in either the weight loss (Model 2) or weight gain (Model 4) subgroups. In the no weight change subgroup, the magnitude of the partial regression coefficient reflected an even larger improvement in cholesterol (-9.8 mg/dl for those with 3+ cycles compared to those with 0, 1 or 2 cycles).

- Similarly, in HDL regression Model 7, having 3 or more cycles compared to having 0, 1 or 2 cycles was associated, only in the weight loss group, with improvements in HDL of 3.4 mg/dl.

The two instances described above where regression analyses showed a greater improvement in total cholesterol with 3 or more cycles were confirmed in cholesterol ANCOVA Models 1A and 3A and in the HDL ANCOVA Model 2B. In these cases, the magnitude of the improvements associated with having three or more weight cycles could be considered clinically significant.

Figures 4 -7 graphically display the results of ANCOVA models based on number of cycles to allow examination of overall patterns of changes in risk factors with progressive degrees of weight cycling. The charts illustrate that there is not evidence for a beneficial effect of weight cycling. Although there are instances where higher degrees of weight cycling are associated with larger improvements in risk factors than lower degrees of cycling, there are also

instances where higher numbers of cycles are associated with smaller improvements. The lack of consistency in patterns of change in risk factors is even more obvious when weight cycling is expressed in terms of SEE tertile and as number and size of cycles (data not presented graphically). In other words, there is no dose-response relationship of progressively greater improvements with increasing measures of cycling in any risk factor, despite careful structuring of data analyses to allow detection of dose-response relationships should they be present. .

Figure 4 shows a significant improvement in total cholesterol for men with 3 or more cycles in the no weight change group. The pattern of changes in that particular subgroup of the population is consistent with the presence of a threshold effect. If there were a threshold effect for weight cycling, this would mean that weight cycling is beneficial but only when the magnitude of the cycling is great enough to produce the "benefit." Careful examination of all the data, however, make it clear that there is no such threshold effect. If there were, it would be observed in other subgroups and for other risk factors.

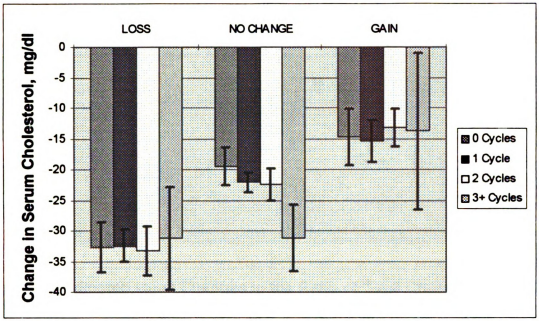

Figure 4 - Adjusted Mean Changes in Total Cholesterol (and 95% Confidence Interval) by Net Weight Change Group and Number of Weight Cycles, MRFIT SI Group

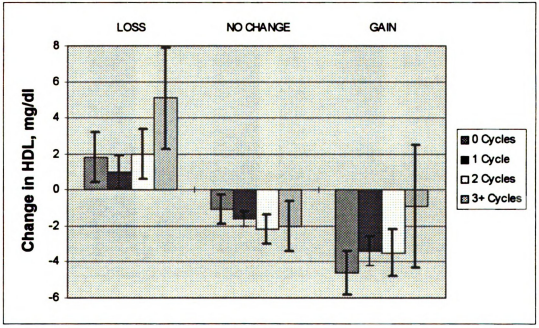

Figure 5 - Adjusted Mean Changes in HDL (and 95% Confidence Intervals) by Net Weight Change Group and Number of Weight Cycles, MRFIT SI Group

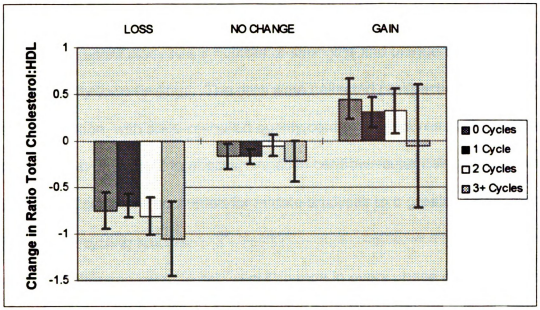

Figure 6 - Adjusted Mean Changes in the Ratio of Total Cholesterol to HDL (and 95% Confidence Interval) by Net Weight Change and Number of Weight Cycles, MRFIT SI Group

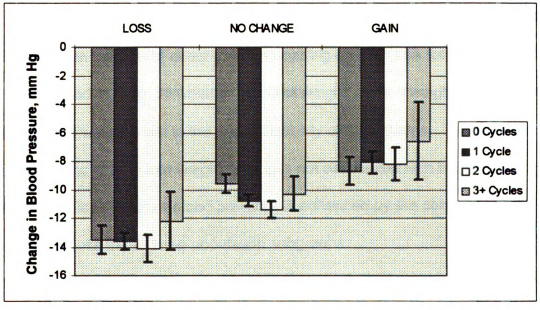

Figure 7 - Adjusted Mean Changes in Diastolic Blood Pressure (and 95% Confidence Intervals) by Net Weight Change Groups and Number of Weight Cycles, MRFIT SI Group

Strengths of the Study

The present study has a number of strengths and unique aspects which lend credibility to its findings. The data were collected prospectively on a very large population, with state-of-the-art quality control procedures in place. Other factors known or thought to affect changes in cardiovascular risk factors were documented and were accounted for in data analyses to a greater extent than in other weight cycling studies.

The attention given to net weight change in every phase of data analysis is a strong feature of this research. Weight loss and weight gain have been shown repeatedly to predict changes in CVD risk factors. In this population the strongest predictor for change in risk factors other than baseline levels of the risk factors was net weight change, and each net weight change group was different from every other one with respect to most variables used in analysis. Verifying that the lack of effect of weight cycling on each risk factor examined was observed in subjects whether they lost weight, gained weight, or remained at the same weight adds to the generalizability of the findings. The external validity of the finding that weight cycling is not associated with detrimental effects on blood lipids or blood pressure is enhanced by the consistency of findings across these three population subgroups.

The internal validity of the finding that weight cycling was not associated with detrimental effects on blood lipids or blood pressure in the MRFIT SI population is enhanced by the consistency of findings with two different statistical approaches (Analysis of Covariance and Multiple Regression) and

with five different ways of measuring weight cycling (number of cycles, cycler vs. non-cycler, number / size of cycles, SEE and various dummy variables in the regression analysis).

The documentation of weight is more complete than in any other study of weight cycling, with weight measured at 4-month intervals over 6 years. Other studies of weight cycling have used as few as 3 weights to construct an index of weight cycling, and intervals between weight measurements have ranged from a minimum of 1 year to more than 5 years.

The measures of weight cycling used in this research are more reliable and meet more of the criteria for validity than measures used in other studies:

- The reliability of the weight measurements upon which the documentation of weight cycling was based was verified via calibration of scales, training of personnel and testing for consistency between technicians.
- The weight measurements on which documentation of cycling is based are close enough together and are numerous enough to detect patterns in weight changes.
- Because the actual number of cycles are counted and the SEE is used, weight changes due to steady losses or gains are differentiated from changes due to cycling. This is not the case in other studies which used standard deviation of weight or coefficient of variability as the measure of weight cycling.
- By combining number of cycles and SEE in one measure of cycling, large cycles are differentiated from small cycles, maximizing the possibility of detecting dose-response effects should they be present.

The exclusion of subjects without a nearly-complete set of 4-month interval weights resulted in fewer subjects for analysis, but increased confidence that the measures of weight change and weight cycling used for analysis reliably reflected actual weight patterns in the study population. Dropping the UC group should place no limitations on generalizability of the data, because the randomization procedures employed in the study protocol assured that the SI group and the UC group were essentially identical. This was verified by T tests comparing the UC group with the SI group. The two groups were not found to be significantly different with respect to any baseline characteristic considered.

Another strength of this study of weight cycling is that the weight changes which were documented are with little doubt the result of voluntary weight loss efforts rather than illness. Lack of verification that weight changes were volitional has been a limitation of many studies of weight change and morbidity/mortality. In the MRFIT SI population, intensive intervention on weight that was part of the study protocol assured that there would be weight losses, and the lack of long-term effectiveness of any weight loss intervention assured that there would also be weight regains. Exclusion of individuals with the conditions likely to cause weight loss, plus control in regression analyses for the presence of conditions and medications associated with weight changes effectively eliminated the effects of illness on weight change.

Limitations of the Study

Because of the differences in exclusions and in categorization of men by cycling status, there is no assurance that the subjects classified as weight

cyclers in the present study were identical with the subjects classified as cyclers and found to be at high risk of death in the mortality study by Blair et al.[1] Although it would be ideal if the study populations had been identical, the discrepancy does not invalidate the present study of effects of weight cycling on risk factors.

The results of this study cannot be generalized to as great a degree as would be desired. The population studied consisted only of men at high risk of heart disease, who were probably somewhat healthier than average. There was little ethnic diversity among the population. In the SI group, there were too few minorities other than African Americans to allow separate analyses by ethnicity. The 342 African Americans in the SI group constituted only 7% of the sample. Although race was used as a blocking variable in all models, and no differences were found in the effects of weight cycling in African Americans vs. Caucasians, there is less confidence in the results for African Americans than for Caucasians. Given the high prevalence of hypertension in the African American community, inability to generalize to African Americans is an important limitation of the study. No conclusions can be drawn about the effects of weight cycling on CVD risk factors for women.

The reliability of the blood lipid outcome measures is somewhat limited by the fact that baseline and year 6 blood lipid values were each based on only one measurement. Considering the fact that within-person fluctuations of serum cholesterol of over 20% have been reported for the majority of individuals in whom this has been measured,[89, 90] and the average change in serum

cholesterol found in the MRFIT SI group was only 8.4%, it would have been highly appropriate to base decisions as to whether cholesterol concentrations have changed on the average of several measurement, with the samples taken on different days.[164, 165]

However, this procedure was not included in the MRFIT protocol. Baseline and subsequent values for cholesterol concentrations were each based on one fasting blood sample. To obtain a more representative measure of baseline cholesterol, averaging of the total cholesterol values at baseline and at the first 4-month visit was considered, but this approach was rejected because the first intensive interventions were initiated at the final screening visit, so the cholesterol concentration at the 4-month visit could not be considered baseline data. Diurnal variations in cholesterol may not have been an issue, because the blood samples were taken in the fasting state, presumably collected early in the day. Month or season of the year may have been somewhat consistent because all study participants were invited for data visits every 4 months, although strict observance of anniversary dates was not completely enforceable, given the many factors involved in scheduling clinic appointments for 12,000 individuals in 22 different centers.

Dropping SI members with more than 3 missing weight measurements had some potential for introducing bias, since, as shown in Table 33, those dropped were younger, at lower risk at baseline, and probably less compliant than those retained. Level of compliance would be a crucial factor mediating the effects of weight cycling on CVD risk factors. There is no reason to assume,

however, that the subjects missing more than 3 weights were the only subjects who were less than perfect in their compliance with the MRFIT regimen (as evidenced, for example, by the 800 who gained weight over the course of the trial). Level of compliance was controlled for, indirectly, by including nutrition, smoking, and exercise variables in the models.

Although some mental health information was available in the data set, no mental health variables were included in the analysis. The rationale for leaving them out was that none of the variables available was associated with mortality in this population. In retrospect, it would have been interesting to pursue whether any mental health factors met the criteria for inclusion in ANCOVA or regression models. This remains a possibility for future research.

Although the documentation of weight available for defining weight cycles is superior to that used in any other study of weight cycling, it should be noted that the number of weight cycles may have been underestimated in some individuals. Measurements at 4-month intervals made it possible to document any weight cycles which occurred over a period of 8 months or longer. It is biologically possible for an individual to lose and regain 5% of body weight in as short a time interval as two months. [66, 157, 158, 159] Such rapid weight changes would have been possible but unlikely in the MRFIT SI population.

There are three important limitations in the measurement of weight cycling in this study. One is the exclusion of any indicator of the duration of each weight cycle. For example, a loss and regain of 20 pounds within a period of 8 months was indistinguishable from an identical weight loss and gain that occurred over a

6- year period. A second limitation in the documentation of weight cycling is lack of differentiation between cycles characterized by initial weight loss followed by regain and cycles that begin with a weight gain followed by a loss. A cycle resulting from loss of weight previously gained could have more positive health implications than a cycle resulting from loss and regain. A third limitation in the measurement of weight cycling is restriction of the definition of a weight cycle to 5% weight changes. A 5% change in weight was chosen to define a weight cycle because of the increased mortality noted in this population with weight cycles of that magnitude.[1] However, It would be interesting to know whether cycles of 10% would have yielded different results. These limitations could potentially be overcome using sophisticated pattern analysis techniques to define weight cycling patterns; this would be a valuable avenue for future research.

Control for nutrient intakes which may have affected outcomes was not as strict as would have been desired. To statistically control for effects of nutrients on blood cholesterol changes, it would have been ideal to determine each subject's change in intake of selected nutrients, because validated prediction equations have been developed to predict change in blood cholesterol from changes in dietary cholesterol, saturated fats and polyunsaturated fats.[166,167]

Unfortunately, it was not possible to evaluate individual changes in nutrient intake over time, because the data tapes received from NHLBI included only 24-hour dietary recall data at baseline and at year 6; food frequency data collected on the SI group were not included. A one-day intake of a nutrient is

not representative of "usual intake" for an individual.[80] Because it was not possible to calculate changes in nutrients, the decision was made to calculate "typical" intakes over the trial. It is recognized that the average of three 24-hour intakes of a nutrient, taken at 1-year intervals is not an ideal marker for food consumption. This limitation may explain the low Pearson correlation coefficients observed between all nutrients and changes in blood lipids and blood pressure.

Another factor that could have contributed to low correlations between nutrient intakes and outcomes was incompleteness of the nutrient data bases available at the time nutrient intake data was coded for the MRFIT study. The University of Minnesota staff who were responsible for the data base placed greatest emphasis on food composition related to fat intake, since the diet-heart hypothesis at that time centered on the fat content of the diet. Only in recent years have food composition data become available to allow the development of more complete data bases for nutrients such as Vitamin E, folic acid, and dietary fiber.

An additional shortcoming in the control for nutrient intake was failure to include the nutrients folic acid and Vitamin C, which have been recognized recently as having potential roles in the etiology of heart disease.[80, 168]

One measure of CVD risk which has recently been recognized as an important predictor of CVD morbidity and mortality is waist to hip ratio. There is very strong epidemiological evidence that body fat distribution is a more powerful predictor for the morbidity and mortality associated with obesity than is

body weight.[169, 170] In studies where body fat distribution is considered along with body weight, fat distribution correlated more strongly with cardiovascular risk factors and mortality. Given the fact that individuals with a history of weight cycling have been shown to have higher waist to hip ratios than those without such a history,[117] it is unfortunate that information about waist to hip ratio was not included in the data set.

Low Correlations of Outcomes with Lifestyle Factors

A surprising observation was that many of the factors believed to affect the CVD risk factors studied in this research that were documented in the data set were not as highly correlated with the outcomes as had been expected. The extent to which the documentation available reflected actual lifestyle practices was not always as great as would have been desired.

The state of the art for documentation of physical activity patterns leaves much to be desired. Average minutes of leisure time physical activity over an entire year, based on one recall at the end of that year, requires complex thinking and detailed memory retrieval on the part of subjects, and could be expected to include inaccurate information. Additionally, the researcher's decision to use LTPA reported at year 1, based on the fact that patterns of LTPA in the MRFIT population remained relatively constant from year 1 through year 6,[160] could be called into question. Exercise patterns closer to the time of final measurement of each risk factor or changes in exercise patterns between baseline and year 6 may have had more of an impact on changes in risk factors than patterns during the first year of the study. These factors may account for

the low correlations observed between physical activity variables and outcomes, and may explain why the physical activity variable most correlated with outcomes was the subjective measure of exercise, exercise opinion at year 6.

Exercise opinion at year 6 was included in several ANCOVA models and in several regression models. In regression models, because it was a categorical variable, it had to be converted to dummy variables in order to be used. Using the dummy variable of greatest interest (0=much less exercise than others, 1 = much more exercise than others) resulted in dropping from analysis the majority of subjects with intermediate levels of physical activity, thus reducing the power of the statistical tests. Even so, adding exercise opinion to the regression models did not alter the results of the analysis.

It was a disappointment that the measure of actual physical fitness selected for analysis - the number of minutes each subject was able to continue the graded exercise test (exercise duration) - was not available in the data set received from the National Heart, Lung and Blood Institute except at baseline. Exercise duration at year 6 and change in exercise duration from baseline to year 6 would have been desirable measure of fitness, and may have been more highly correlated with outcomes.

It was surprising that the smoking measures used for this analysis contributed very little to the variability in outcomes. For total cholesterol, mean number of cigarettes per day was not significant in any model. For HDL, cigarettes per day were significant only for the weight gain group, in which smoking was associated with a small positive effect. For both blood pressure

and the ratio of HDL to total cholesterol, smoking was associated with small improvements in outcomes. The magnitude of the positive effect was small. For example in the blood pressure regression models, for each additional cigarette smoked, blood pressure was reduced by .03 mm Hg. In the HDL regression models, for every additional cigarette, weight gainers saw an average increase in HDL of 0.04 mg/dl.

These counter-intuitive observations are not completely inconsistent with other studies of risk factor changes in the MRFIT SI population. It has previously been reported by Caggiula et al.[151] that among MRFIT SI group members, smokers experienced smaller reductions in cholesterol than did non-smokers, but analysis of dietary intake patterns revealed that the diminished cholesterol response was largely due to poorer dietary compliance by smokers. Gerace et al.[146] reported that change in smoking status by MRFIT SI Group members was not independently associated with change in diastolic blood pressure, although those who quit smoking did experience an increase in HDL.

Associations of smoking with outcomes may have been higher if outcomes had been documented over shorter time periods, so that shorter-term effects of smoking on outcomes could be observed. It should be noted that the two measures of smoking used in analyses - mean number of cigarettes per day over the entire trial and smoking status during the trial - were more highly correlated with changes in blood pressure and cholesterol than either number of cigarettes per day at the time of the final visit or smoking status at the final visit.

Importance of Net Weight Change in Predicting Outcomes

One of the clearest messages found in this data analysis is that the one factor most highly correlated with changes in blood pressure and blood lipids between baseline and year 6 was net weight change over the same period. Table 9 illustrates this message very clearly - for each outcome, those who lost weight experienced the greatest improvement, those who gained weight experienced the smallest improvement (or the greatest deterioration), and the no change group experienced intermediate changes. For each outcome, each net weight change group was significantly different from every other net weight change group. This is not a startling or new finding, but it adds to the credibility of the data analysis by confirming what has been found in so many other studies.

It had been anticipated that weight change in the final year or weight change in the final 4-month interval of the intervention period would have a higher correlation with outcomes than net weight change. This was found to be true only in the group with minimal weight change, for whom these later weight changes were more predictive of outcome.

What had not been anticipated was the different patterns of correlations between covariates and outcomes seen in the population as a whole compared with each weight change group, illustrated in Tables 35-38 in Appendix E. For example, Table 35 shows that 13 of 24 possible covariates were correlated with change in total cholesterol in the entire non-excluded population, 12 of the 24 were significantly correlated in the weight loss group, while for the no weight

change group and the weight loss group, 8 and 9, respectively, of the 24 were significant. Of the variables significantly correlated, only three variables (highlighted by shading in Table 35) were significantly correlated in the entire population and all 3 subgroups. It could be surmised that the differences in numbers of significant correlations were artifacts due to different numbers of subjects in each group, but this cannot be the whole explanation because the group with the most subjects (no weight change group, with 2,446 subjects) had fewer positive correlations than the weight loss group (1,056 subjects).

A possible interpretation of these differences in patterns of correlation is that the positive effects of diet and exercise on elevated blood pressure and blood lipids are enhanced by weight loss, or blunted by weight gain or failure to lose weight. This is consistent with the finding of Caggiula et al.[151] for the MRFIT SI Group - that the magnitude of the difference in observed cholesterol response between the group losing more than 10 pounds and the group who gained weight was greater than that predicted by the Keys and Hegsted equations.[166, 167] This, again, is not a startling or new finding, but adds to the credibility of the data analysis.

What Accounts for the Increased Mortality Associated with Weight Cycling?

The results of this research do not support the hypothesis that the increased mortality observed among weight cycling males at high risk of heart disease is caused by deleterious effects on blood lipids or blood pressure. The question remains - if weight cycling is causing increased mortality, by what

mechanisms could this be occurring? Most speculation as to possible mechanisms revolves around negative consequences of either the weight loss or the weight gain phase of the weight cycle.

Damage during weight loss: Perhaps weight cyclers sustain damage to cardiac tissue during the weight loss phases of each cycle. It was shown in investigations of deaths from very low calorie liquid protein diets in the 1970's that rapid, extensive weight loss is associated with atrophy of cardiac tissue.[171] Perhaps repeated bouts of weight loss cause cumulative damage to cardiac muscle, eventually leading to lethal arrhythmias such as those seen in the liquid protein deaths. Another way weight loss could cause cumulative harm was suggested by popular nutrition writer of the 1950's, Adelle Davis,[172] who cautioned against extreme weight loss because environmental pollutants that are potentially cancer-promoting or cardiotoxic such as DDT are stored in fat. When fat stores are mobilized during weight loss, these toxins become more concentrated in the remaining adipose tissue, and therefore achieve higher concentrations in the blood. Data do not exist to confirm this mechanism.

In a similar vein of thought, weight loss may be associated with increase in some unrecognized risk factor for CVD, such as changes in platelet function, increases in concentrations of arachidonic acid, or depletion of omega-3 fatty acid reserves.[173, 174] It is known that weight loss is accompanied by some demineralization of bones, thus increasing the potential for osteoporosis in older women. Osteoporosis is sometimes called "the silent killer," because it leads to hip fractures in older women which precipitate a chain of events leading to death

within a few months of the fracture.[175] Some of the increases in all-cause mortality observed in weight cycling women could be attributable to increased fractures and subsequent complications.

A more direct link between the weight loss phase of weight cycling and increased mortality risk from cycling could be the use of health-threatening methods of weight loss, such as those documented by Zimmerman et al.[44]

Damage during weight gain or during periods of elevated body weight: Others suggest that it is the weight gain phase that could be the culprit. Keyes et al. speculated that irreversible atherogenesis occurs during periods of weight gain which is not offset by benefits incurred during weight loss.[176] Cutter conjectured that, if people who are heavier are more likely to weight cycle, the increased mortality associated with weight cycling could be the result of increased risk that was incurred while weight was elevated.[177]

Does Weight Cycling Really Cause Increased Mortality?

One explanation for the lack of association between risk factors for mortality and measures of weight cycling is that, given the many limitations of the published studies of weight cycling and mortality, it may be that the increased mortality found to be associated with weight cycling is an artifact, and that the association would not be found if some as yet unidentified factor were identified and quantified. The most vocal proponents of this view point out that none of the studies of weight cycling and mortality have been able to differentiate with 100% certainty those whose weight cycles were the result of voluntary dieting (with subsequent weight regain) from those whose weight

varied because of illness. If this were clarified, it is argued, no ill effects of weight cycling would be found.

It is tempting to embrace this point of view, given the methodological problems inherent to the study of weight cycling, and given the absence of a documented mechanism whereby cycling could increase risk of dying. However, the fact that increased mortality has been found in so many different populations by different researchers using different definitions of weight cycling and different approaches to controlling for illness makes it impossible to dismiss the possibility that weight cycling may be detrimental to health.

As long as the situation remains as it is in the United States where 40% of adult women, 20% of adult men, and ever-increasing numbers of children are dieting,[8] it is critical that any health effects from weight cycling be clearly identified.

Future Research Directions

As mentioned above, it is critical that the question of whether weight cycling is detrimental to health be clarified. Kuller and Wing[178] have suggested that secondary analysis of existing data sets will not be helpful in gaining insights to this question. They recommend that future studies need to focus first on the reasons for weight loss and weight cycling, and then on the metabolic and health consequences. Ongoing clinical and longitudinal trials should collect data in a way that would permit elucidation of the reasons for weight loss and weight cycling. Methods used to induce weight loss should also be documented,

inasmuch as use of health-threatening weight loss practices could make independent contributions to mortality risk.

An aspect of weight cycling research which merits much more attention is the relationship among psychological status, stress, weight cycling, and mortality. A few studies have demonstrated that individuals with a history of weight cycling showed more signs of psychological pathology than those without such a history, independent of weight.[179] These studies, along with the studies showing accelerated atherogenesis in socially-stressed primates,[112,113] raise interesting possibilities for identifying causal pathways. The relatively new research field of psychoneuroimmunology is building a body of evidence that emotional states directly affect the immune system. Given cultural norms of unrealistic slenderness and pervasive discrimination against overweight individuals, the mental health aspects of weight loss and regain and their possible contributions to CVD and other causes of mortality should be examined more closely. The MRFIT data set is not ideal for examining this issue, because it includes only men and includes a limited range of psychosocial data.

The MRFIT data set, however, holds the potential for addressing several other questions related to possible effects of weight change on health. It would be most useful to look at the effects of one complete weight cycle on the CVD risk factors examined in this study. Specifically, after loss and complete regain of at least 5% of body weight, are an individual's blood lipids and blood pressure the same, higher, or lower than before the weight cycle began? Are the same patterns of changes in risk factors seen in a second and third weight cycle as in

the first? Is the rate of change in CVD risk factors the same as the rate of change in weight? Is the rate the same during weight loss as during weight gain?

Another crucial weight issue - the question of how best to maintain weight loss - could also be addressed with this data set. Conventional wisdom holds that gradual weight loss is more likely to be associated with longer-term weight maintenance than rapid weight loss. This belief could easily be tested with the data already extracted from the MRFIT data base.

The final area of future research suggested by the results of this study is validation of the finding of increased mortality among weight cyclers identified in the major studies of weight cycling, including the study by Blair and colleagues[1] of mortality in the MRFIT population. It would be most interesting to learn whether the increased mortality seen with weight cycling found in other studies would still be evident if the analyses were repeated using the more reliable and valid measures of weight cycling developed for this research.

SUMMARY AND CONCLUSION

The hypothesis that men who weight cycled experienced smaller improvements in blood lipids and blood pressure compared to men who did not weight cycle was not supported by the findings of this research, whether weight cycling was expressed in terms of number of cycles, SEE, or as a combination of these. The lack of association of weight cycling measures with CVD risk factors was observed whether individuals gained weight, lost weight, or experienced minimal weight change. If weight cycling caused increased mortality risk in the MRFIT SI Group, it does not appear that the increased mortality was mediated by effects on total serum cholesterol, HDL, the ratio of total cholesterol to HDL or diastolic blood pressure. This finding could be generalized to a population of Caucasian middle-aged males at high risk for heart disease who are taking measures to reduce their risk factors. It cannot be generalized to younger men, women, or minorities, on whom further research is warranted.

APPENDICES

APPENDIX A : UCRIHS Approval for Research

MICHIGAN STATE
UNIVERSITY

September 15, 1995

TO: Karen Petersmarck
1557 Hillside
Okemos, Mi 48864

RE: IRB#: 93-449
TITLE: EFFECT OF WEIGHT CYCLING ON CHOLESTEROL AND BLOOD PRESSURE IN THE MULTIPLE-RISK FACTOR INTERVENTION TRIAL POPULATION
REVISION REQUESTED: N/A
CATEGORY: 1-E
APPROVAL DATE: 09/15/95

The University Committee on Research Involving Human Subjects'(UCRIHS) review of this project is complete. I am pleased to advise that the rights and welfare of the human subjects appear to be adequately protected and methods to obtain informed consent are appropriate. Therefore, the UCRIHS approved this project and any revisions listed above.

RENEWAL: UCRIHS approval is valid for one calendar year, beginning with the approval date shown above. Investigators planning to continue a project beyond one year must use the green renewal form (enclosed with the original approval letter or when a project is renewed) to seek updated certification. There is a maximum of four such expedited renewals possible. Investigators wishing to continue a project beyond that time need to submit it again for complete review.

REVISIONS: UCRIHS must review any changes in procedures involving human subjects, prior to initiation of the change. If this is done at the time of renewal, please use the green renewal form. To revise an approved protocol at any other time during the year, send your written request to the UCRIHS Chair, requesting revise approval and referencing the project's IRB # and title. Include in your request a description of the change and any revised instruments, consent forms or advertisements that are applicable

PROBLEMS/ CHANGES: Should either of the following arise during the course of the work, investigators must notify UCRIHS promptly: (1) problems (unexpected side effects, complaints, etc.) involving human subjects or (2) changes in the research environment or new information indicating greater risk to the human subjects than existed when the protocol was previously reviewed and approved.

If we can be of any future help, please do not hesitate to contact us at (517)355-2180 or FAX (517)432-1171.

Sincerely,

David E. Wright, Ph.D.
UCRIHS Chair

DEW:kaa/lcp

cc: Jenny Bond
Howard Teitelbaum

OFFICE OF
RESEARCH
AND
GRADUATE
STUDIES

University Committee on Research Involving Human Subjects (UCRIHS)

Michigan State University
232 Administration Building
East Lansing, Michigan
48824-1046

517/355-2180
FAX: 517/432-1171

Appendix B: Response to Freedom of Information Request for MRFIT Data

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

July 2, 1992

Karen Petersmarck, M.P.H., R.D.
1557 Hillside Drive
Okemos, Michigan 48864-2319

Dear Ms. Petersmarck:

I am writing in response to your request for selected MRFIT data tapes and documentation, to be used in your pursuit of a doctoral degree from Michigan State University. Staff of our Biostatistics Research Branch have determined that 8 tapes, covering baseline and tri-annual followup visits, will be required to meet your need for all of the Special Intervention weight data over the course of the trial. These tapes will also provide age and height; blood lipids, uric acid and glucose levels; smoking history, leisure time physical activity, use of cholesterol lowering drugs, and some dietary data; and most but not all of the data on blood pressure and antihypertensive drugs. Extensive dietary data are contained on other tapes.

It will take 1-2 months to fill your request, due to the need to remove certain identifiers and to photocopy a lot of documentation. The cost of the data set will be $50 per tape for a total of $400. Payment should be in the form of a check make out to "DHHS/NIH".

Our understanding with regard to release of these data to you, and the faculty members you named, are as follows:

- the data will be treated and protected as confidential medical records, no effort will be made to identify participating individuals, and contacts with MRFIT centers about their data in this data set will only be made on terms agreed upon with NHLBI, and

- you will not make the data set or portions of it available outside of your research group at Michigan State University without our concurrence.

I would appreciate a note back from you agreeing to these terms. Please also indicate the person or office that will be responsible for payment.

Finally, as you know, the publication of MRFIT results on behalf of the original Research Group is under the direction of an Editorial Committee, chaired by Dr. Marcus Kjelsberg at the University of Minnesota. On behalf of the Committee, I would like to request a confidential courtesy copy of any manuscript that is written as a result of the work you plan to undertake.

If you need any further information, you can contact me at (301) 496-2465, or Dr. Margaret Wu or Ms. Barbara Geraci, at (301) 496-5905.

Sincerely,

Jeffrey A. Cutler, M.D., M.P.H.
Chief, Prevention and Demonstration
Research Branch
Division of Epidemiology and
Clinical Applications

cc: Dr. M. Wu
Ms. B. Geraci

APPENDIX C: Sample, SAS Program to Extract MRFIT Data from Magnetic Tapes

```
cms tape rew;
LIBNAME DAT XPORT 'ANN1 TRN A';
cms filedef tapein tap1 sl 2 (lrecl 2100 blksize 23100 recfm fb;
data dat.mrfitan1;
infile tapein;
input

ID $ 3-13 WT1 83-86 BMI1 1820-1822 RWT1 1817-1819 BPTX1 399 BPTX21
422 BPG1 1946 BP1 74-76 BPRX1 414 DIUC1 1841-1843 DIUH1 1844-1846
CHOL1 907-911 CHOLA1 1784-1786 LIPRX1 375 TG1 913-917 SMOKE1 119
CIGS1 128-129 CIGD1 1832-1833 EXD1 1417-1420 EXO1 717 ALC1
1876-1878 DIETW1 722 DIETC1 724 MISS1 437 UWL1 559 GLC1 943-947
DATE1 148-153 DAYS1 1869-1871 UA1 919-923 HAP1 708 LE1 1899-1900
KNUT1 1901-1902 COF1 870-871 TEA1 876-877 COLA1 882-883 WT14
1081-1084 BMI14 1967-1969 RWT14 1964-1966 BPG14 1963 BPTX14 1068
BPTX214 1080 BP14 1133-1135 BPRX14 1173 CHOL14 965-969 SMOKE14
1136 CIGS14 1144-1145 CIGD14 1974-1975 NUTAD14 1170 DATE14
1070-1075 DAYS14 1982-1984 TG14 971-975 UA14 977-981 GLC14 855-859
WT18 1224-1227 BMI18 2018-2020 RWT18 2015-2017 BPG18 2014 BPTX18
1223 BP18 1276-1278 BPRX18 1316 CHOL18 1024-1028 SMOKE18 1279
CIGS18 1287-1288 CIGD18 2025-2026 NUTAD18 1313 DATE18 1017-1022
DAYS18 2033-2035 TG18 1030-1034 UA18 1036-1040 GLC18 1060-1064
MHSP1 554 MHTS1 556 MHBS1 557 MHBED1 563 RXA1 372 RXB1 373 RXC1
374 RXD1 375 RXFG1 376 RXH1 377 RXI1 378 RXJ1 379 RXK1 380 RXL1 381
RXM1 382 DXCA1 256 DXCB1 257 DXCC1 258 DXCD1 259 DXCE1 260
DXCF1 261 DXCG1 262 DXCH1 263 DXCI1 264 DXCJ1 265 DXCK1 266
DXCL1 267 DXMNA1 268 DXMNB1 269 DXMNC1 270 DXMNE1 272 DXDM1
273 DXEB1 274 DXEC1 275 DXED1 276 DXEE1 277 DXEF1 278 DXEG1 279
DWEH1 280 DXMDA1 283 DXMDB1 284 DXMDC1 285 DXMDD1 286
DXNDE1 287 DXMDF1 288 DXNA1 289 DXNB1 290 DXMSA1 291 DXNSB1 292
DXRA1 293 DXRB1 294 DXRC1 295 DXRD1 296 DXDA1 297 DXDB1 298
DXDC1 299 DXDD1 300 DXDE1 301 DXGA1 303 DXGB1 304 DXGC1 305
DXGD1 306 DXGE1 307 DXHA1 308 DXHC1 309;
run;
```

APPENDIX D: SAS Program for Counting Weight Cycles

Written by Jay McClellan, M.S.E.E.

```
* Read in the weight data from the SAS data set siclean5.sd2;
libname karen 'c:\data2';
options nocenter;
data one;
set karen.siclean5;
* Define the weight array;
array WT(19) WTB WT04 WT08  WT1 WT14 WT18
          WT2 WT24 WT28  WT3 WT34 WT38
          WT4 WT44 WT48  WT5 WT54 WT58 WT6;
* Define the number of weights;
count = 19;
* Define the transition threshold amount;
thresh = WTMEAN * 0.05;
* Set peak & valley counts to zero;
peaks = 0; valleys = 0;
* Initial reference weights are the first weight in the set;
hirefwt = WT(1);
lorefwt = WT(1);
* Initial state is WAITING;
state = 0;
* Loop over all weights in the set (after the first);
do sample=2 to count;
  * Process the sample only if it's not a missing data point (.);
 if WT(sample) ne . then do;
   select (state);
     * If the state is WAITING, looking for a transition from start weight;
     when (0) do;
       * Set the high & low reference weights to the max & min so far;
       lorefwt = min(lorefwt, WT(sample));
       hirefwt = max(hirefwt, WT(sample));
       * Is the weight sufficiently above the low reference weight?;
       if WT(sample) >= lorefwt + thresh then
         do;
           * Yes - start CLIMBING;
           state = 1;
         end;
       * Is the weight sufficiently below the high reference weight?;
       if WT(sample) <= hirefwt - thresh then
         do;
```

SAS Program to Count Weight Cycles, continued

```
            * Yes - start FALLING;
            state = -1;
          end;
      end;
      * If the state is CLIMBING, found a positive excursion - subject is gaining
  weight;
      when (1) do;
        * Set the reference weight to the maximum seen in this excursion;
        hirefwt = max(hirefwt, WT(sample));
        * Is the current weight sufficiently below the reference weight?;
        if WT(sample) <= hirefwt - thresh then
          do;
            * Yes - got a cycle, so increment the peak count;
            peaks = peaks + 1;
            * Set this as the new reference weight;
            lorefwt = WT(sample);
            * Transition to the FALLING state;
            state = -1;
          end;
      end;
      * If the state is FALLING, found a negative excursion - subject is losing
       weight;
      when (-1) do;
        * Set the reference weight to the minimum seen in this excursion;
        lorefwt = min(lorefwt, WT(sample));
        * Is the current weight sufficiently above the reference weight?;
        if WT(sample) >= lorefwt + thresh then
          do;
            * Yes - got a cycle, so increment the valley count;
            valleys = valleys + 1;
            * Set this as the new high reference weight;
            hirefwt = WT(sample);
            * Transition to the CLIMBING state;
            state = 1;
          end;
      end;
    end;
  end;
end;
* The number of cycles is the larger of peaks or valleys;
cycles = max(peaks, valleys);
run;
```

APPENDIX E: Tables Showing Correlation Coefficients for Selected Variables with Each Outcome

Table 35 - Correlation Coefficients for Selected Variables with Net Change in Total Serum Cholesterol for All Non-excluded Subjects and by Net Weight Change Group, MRFIT SI Group

Variables	All Non-Excluded [a] (n=4,302)	Weight Loss (n=1,056)	No Wt. Change (n=2,446)	Weight Gain (n=800)
Age	-.05	n.s.	-.04	-.13
Race	n.s.	n.s.	n.s.	n.s.
Baseline Cholesterol	-.42	-.45	-.42	-.38
Wt. Change, Final 4 Months.	.11	n.s.	.11	n.s.
Net Weight Change	.19	.15	.O8	n.s.
Relative Weight, Baseline	-.05	n.s.	n.s.	-.12
Weight, Baseline	-.03	.06	n.s.	-.11
Alcohol Intake	n.s.	n.s.	n.s.	n.s.
Caffeine Intake	n.s.	n.s.	n.s.	n.s.
Calcium Intake	n.s.	-.14	n.s.	n.s.
Cholesterol Intake	.06	.06	.06	n.s.
% Calories from Fat	n.s.	n.s.	n.s.	n.s.
Water-soluble Fiber Intake	-.10	-.21	n.s.	-.07
Iron Intake	-.04	-.08	n.s.	n.s.
P:S Ratio	-.12	-.16	-.07	-.11
Sodium Intake	n.s.	n.s.	n.s.	n.s.
Vitamin E Intake	-.08	-.12	-.04	n.s.
Exercise Duration	n.s.	n.s.	n.s.	.07
Exercise Opinion, Year 6	-.05	n.s.	-.04	n.s.
LTPA, Heavy	n.s.	n.s.	n.s.	n.s.
LTPA, Total	n.s.	-.08	n.s.	n.s.
Physical Activity Quintile, Heavy	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Total	n.s.	-.08	n.s.	n.s.
Cigarettes per Day	.10	.06	.06	.09

Table 35 (cont'd)

[a] Excluded: Subjects missing 4 or more weight measurements, and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

Table 36 - Correlation Coefficients for Selected Variables with Net Change in HDL for All Non-excluded Subjects and by Net Weight Change Group, MRFIT SI Group

Variables	All Non-Excluded [a] (n=4,302)	Weight Loss (n=1,056)	No Wt. Change (n=2,446)	Weight Gain (n=800)
Age at Baseline	n.s.	-.06	n.s.	n.s.
Baseline Serum Cholesterol	n.s.	n.s.	n.s.	n.s.
Baseline Plasma Cholesterol	-.04	n.s.	-.07	-.07
Baseline HDL-Cholesterol	-.40	-.33	-.40	-.49
Wt. Change, Final 4 Months	n.s.	n.s.	.05	n.s.
Net Weight Change	-.18	-.09	-.06	n.s.
Relative Weight, Baseline	n.s.	n.s.	n.s.	n.s.
Alcohol Intake	n.s.	.09	n.s.	n.s.
Caffeine Intake	.08	.07	.08	.12
Calcium Intake	n.s.	n.s.	n.s.	n.s.
Cholesterol Intake	.04	n.s.	n.s.	.11
% Calories from Fat	.04	n.s.	.06	.09
Water-soluble Fiber Intake	n.s.	n.s.	n.s.	n.s.
Iron Intake	n.s.	n.s.	n.s.	n.s.
P:S Ratio	n.s.	n.s.	n.s.	n.s.
Sodium Intake	n.s.	n.s.	n.s.	n.s.
Vitamin E Intake	.04	n.s.	.05	n.s.
Exercise Duration at Baseline	n.s.	n.s.	n.s.	n.s.
Exercise Opinion, Year 6	.07	.07	n.s.	n.s.
LTPA, Heavy	n.s.	n.s.	n.s.	n.s.
LTPA, Total	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Heavy	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Total	n.s.	n.s.	n.s.	n.s.
Cigarettes per Day	.07	.09	.10	.16

[a] Excluded: Subjects missing 4 or more weight measurements, and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

Table 37 - Correlation Coefficients for Selected Variables with Net Change in Ratio of Total Plasma Cholesterol to HDL for All Non-excluded Subjects and by Net Weight Change Group, MRFIT SI Group

Variables	All Non-Excluded [a] (n=4,302)	Weight Loss (n=1,056)	No Wt. Change (n=2,446)	Weight Gain (n=800)
Age at Baseline	n.s.	n.s.	n.s.	n.s.
Baseline Serum Cholesterol	-.10	-.13	-.09	n.s.
Baseline Plasma Cholesterol	-.18	-.22	-.16	-.10
Baseline HDL	.30	.35	.30	.23
Wt. Change, Final 4 Months	.04	n.s.	n.s.	n.s.
Net Weight Change	.23	.15	.09	n.s.
Relative Weight, Baseline	-.03	n.s.	n.s.	n.s.
Weight, Baseline	-.05	n.s.	n.s.	n.s.
Alcohol Intake	n.s.	n.s.	n.s.	n.s.
Caffeine Intake	-.06	-.06	-.09	-.07
Calcium Intake	n.s.	-.07	n.s.	n.s.
Cholesterol Intake	n.s.	n.s.	n.s.	-.09
% Calories from Fat	n.s.	n.s.	n.s.	n.s.
Water-soluble Fiber Intake	-.03	n.s.	n.s.	n.s.
Iron Intake	-.05	-.06	n.s.	n.s.
P:S Ratio	-.03	n.s.	n.s.	n.s.
Sodium Intake	n.s.	-.07	n.s.	n.s.
Vitamin E Intake	-.06	-.08	n.s.	n.s.
Exercise Duration at Baseline	n.s.	n.s.	n.s.	n.s.
Exercise Opinion, Year 6	-.07	-.08	n.s.	n.s.
LTPA, Heavy	n.s.	n.s.	n.s.	.09
LTPA, Total	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Total	n.s.	n.s.	n.s.	.09
Cigarettes per Day	-.04	n.s.	-.11	-.13

[a] Excluded: Subjects missing 4 or more weight measurements, and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, Cushing's disease, diabetes, cirrhosis or other liver disease

Table 38 - Correlation Coefficients for Selected Variables with Net Change in Blood Pressure for All Non-excluded Subjects and by Net Weight Change Group, MRFIT SI Group

Variables	All Non-Excluded [a] (n=4,393)	Weight Loss (n=1,060)	No Wt. Change (n=2,514)	Weight Gain (n=819)
Age	-.125	-.099	-.11	-.11
Race	n.s.	n.s.	n.s.	n.s.
Baseline Blood Pressure	-.69	-.66	-.67	-.71
Wt. Change, Final 4 Months	.05		n.s.	
Net Weight Change	.19	.10	.10	n.s.
Relative Weight, Baseline	-.08	n.s.	-.07	n.s.
Alcohol Intake	.05	.09	n.s.	n.s.
Caffeine Intake	.10	n.s.	.09	.16
Calcium Intake	.04	n.s.	.07	n.s.
Cholesterol Intake	.07	n.s.	.05	.07
% Calories from Fat	.04	n.s.	n.s.	.08
Water-soluble Fiber Intake	n.s.	n.s.	n.s.	n.s.
Iron Intake	-.04	n.s.	.06	n.s.
P:S Ratio	-.04	n.s.	n.s.	n.s.
Sodium Intake	n.s.	n.s.	n.s.	n.s.
Vitamin E Intake	-.04	n.s.	-.06	n.s.
Exercise Duration at Baseline	.09	n.s.	.12	.08
Exercise Opinion, Year 6	n.s.	n.s.	n.s.	.08
LTPA, Heavy	n.s.	n.s.	n.s.	n.s.
LTPA, Total	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Heavy	n.s.	n.s.	n.s.	n.s.
Physical Activity Quintile, Total	.04	n.s.	.04	.096
Cigarettes per Day	.19	.11	.16	.20

[a] Excluded: Subjects missing 4 or more weight measurements, and subjects with the following conditions: cancer, unexplained weight loss, thyroid disease, renal disease, angina, primary aldosteronism, Cushing's disease, pheochromocytoma.

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