Voluntary and Involuntary Weight Loss: Associations with Long Term Mortality in 9,228 Middle-aged and Elderly Men

Shlomit Yaari and Uri Goldbourt

Recent studies have suggested that weight loss in middle-aged persons antecedes increased mortality. Therefore, the authors sought to examine the association between changes in body weight and subsequent mortality, according to self-reported dieting status. The authors followed 9,228 men aged 40-65 years in 1963, for whom weight changes between 1963 and 1968 were recorded and extensive clinical, anthropometric, biochemical, and dietary assessments were made. Of these men, 2,471 reported being on a diet when first examined in 1963, and 636 were dieting primarily to lose weight. Mortality follow-up covered an 18-year period (1968-1986). Men who lost 5 kg or more between 1963 and 1968 ("extreme weight losers") exhibited the following age-pooled risks of mortality relative to the stable weight group: for total mortality, 1.36 (95% confidence interval (CI) 1.20-1.55); for all cardiovascular disease mortality, 1.40 (95% CI 1.16-1.69); for all non-cardiovascular disease mortality, 1.33 (95% CI 1.11-1.59); for coronary heart disease mortality, 1.55 (95% CI 1.25-1.93); and for cancer mortality, 0.90 (95% CI 0.65-1.24). After adjustment for differences in coronary heart disease risk factor levels and morbidity between these groups at the end of the weight change period (1968), the excess risks associated with extreme weight loss declined by approximately one third. They declined further if adjustment was made for 1963 (pre-weight-change period) morbidity and risk factor levels. Being on a slimming diet, as reported in 1963, was associated with an approximate doubling of excess mortality in men with extreme weight loss. Weight loss in 1963-1968 coincided with an increased incidence of coronary heart disease and diabetes mellitus and a declining level of serum total cholesterol. This and other studies indicate that both voluntary and involuntary weight loss might be associated with a small increase in the risk of all-cause mortality. Am J Epidemiol 1998;148:546-55.

Recently published reports have indicated, somewhat surprisingly, that persons who reduce their weight over a period of time appear to demonstrate an increased risk of mortality over the long term (1, 2) and that the lowest mortality rates are generally associated with modest weight gains (1). This holds true for all-cause mortality, for coronary heart disease mortality, and for all cardiovascular disease mortality (3, 4). When the first years after the weight change assessment period are omitted in order to account for possibly spurious findings resulting from the effect of latent disease on weight changes preceding mortality (2, 4), the relation persists. Given the persistent finding of increased mortality following weight loss, a question has been raised as to whether this is limited to voluntary weight loss in persons already afflicted with disease or deteriorating health, or whether increased mortality also follows voluntary weight loss in healthy individuals, as well as involuntary weight loss. Using successive weight measurements made in 1963 and 1968 and information on dieting status in 1963, this study attempted to elucidate the association between 5-year weight change and subsequent 18-year mortality.

MATERIALS AND METHODS
Study sample

This report utilizes information collected within the framework of the Israeli Ischemic Heart Disease Study. The Israeli Ischemic Heart Disease Study was a prospective follow-up study of 10,059 men, tenured civil servants and municipal employees, who were aged 40-65 years in 1963, when they were first examined (5). Weight and other characteristics were reevaluated in 95 percent of living participants in 1968. Weight was measured with a beam balance while the participant stood in light street clothes, and
was rounded off to the nearest kilogram. Height was measured to the nearest centimeter while the participant stood without shoes.

**Measurements**

The measure of relative weight used was the body mass index (BMI), defined as weight (kg) divided by height squared (m^2) (6). Weight and height were measured in 10,034 of the 10,059 men included in the first examination. Blood pressure was measured on the right arm with a mercury sphygmomanometer while the subject lay in a comfortably warm room. Detailed procedures followed those outlined by the World Health Organization. Venous blood was collected in a Vacutainer tube (Becton-Dickinson, Rutherford, New Jersey) containing 20 ml of blood without anticoagulant, and serum total cholesterol (nonfasting) was measured by the methods of Anderson and Keys (7). Procedures used in 1963 and 1968 were identical. The final diagnosis of clinically recognized myocardial infarction was made in patients who complained of symptoms suggestive of heart disease who, in addition, had either: 1) an electrocardiogram showing signs of probable or possible infarction (8); 2) autopsy findings consistent with recent myocardial infarction; 3) in hospital subjects, clinical, laboratory, and electrocardiographic findings leading to the diagnosis of probable infarction; or 4) sudden death, i.e., death within 1 hour of the appearance of symptoms in a man who was not hospitalized or confined to bed (8). Complete details on measurements made in the study examinations have been provided elsewhere (9).

Diabetes mellitus was ascertained by testing all subjects and defining those with initial (by the Somogyi-Nelson method) blood sugar levels ≥ 130 mg/dl or those reporting a history of diabetes as “suspect.” “Suspect” individuals with three subsequent blood sugar measurements less than 120 mg/dl and the original definite nondiabetics were defined as being “at risk” for incident diabetes. The latter was determined by the presence of three fasting glucose values ≥ 130 mg/dl (Hagedorn-Jensen method) at follow-up or a positive result of a glucose tolerance test. Further details have been published elsewhere (10). Detailed information on cancer was ascertained from the Israeli Cancer Registry. History of chronic obstructive lung disease and intermittent claudication was assessed by interview. The diagnosis of angina was made on the basis of a questionnaire designed by the study investigators (11) to ensure standard history-taking of chest pain by a number of different physicians. The ability of all of these manifestations of atherosclerosis, as assessed in our study, to predict significantly and importantly morbidity and mortality (12, 13) lends credence to the precision of classification of study subjects.

Of the above 10,034 men, 9,228 survivors (95 percent) participated in the third examination in 1968 and were included in the analysis. A total of 192,369 person-years of follow-up were available for analysis.

**Mortality follow-up**

Information on mortality was derived from the Israeli Mortality Registry. Practically all deaths were accounted for. The cause of each death was classified on the basis of individual determination by a review panel during the 1970s and according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (14), thereafter. Coronary heart disease was considered the underlying cause of death when the ICD-9-CM code was between 410 and 414; additional groupings included mortality due to cardiovascular disease (ICD-9-CM codes 390–459), cancer (ICD-9-CM codes 140–239), and all non-cardiovascular diseases, including cancer.

**Statistical methods**

BMI measured upon initial examination in 1963 was classified into five categories: <22, 22–25, 25–27, 27–30, and ≥30. Among individuals attending both examinations (1963 and 1968), weight change from 1963 to 1968 was classified into five groups: extreme weight loss (≥5 kg), modest weight loss (2–4 kg), stable weight (−1 kg ≤ weight change ≤ 1 kg), modest weight gain (2–4 kg), and extreme weight gain (≥5 kg). Total mortality and cause-specific mortality rates, per 1,000 person years, were calculated for the five weight change ranges in the above categories of BMI.

The pooled risk of coronary heart disease mortality and all-cause mortality in men who had exhibited extreme weight loss (1963–1968), relative to those maintaining a stable weight, was estimated by the Cochran-Mantel-Haenszel method. Stratification was done in five age groups (40–49, 50–59, 60–69, 70–79, and ≥80 years). Age group was determined by age at entry and was advanced individually for each subject in the year the subject reached age 50, 60, 70, or 80 years.

Multivariate analysis of mortality was performed using Cox's life table proportional hazards model, with estimates derived from Breslow's modification for tied data (15). Adjusted relative risks (RR) and 95 percent confidence intervals for death from all causes and from coronary heart disease were estimated for the weight change categories noted above, using the stable weight group as the reference for comparison (RR =
The model incorporated age, smoking status, BMI, serum total cholesterol, and systolic blood pressure, as well as the prevalence of diabetes, cancer, definite angina pectoris, intermittent claudication, and myocardial infarction. In addition, a dummy variable indicating whether or not a subject reported being on a diet in 1963 was introduced into the model. Two alternative analyses were undertaken. One analysis adjusted for 1963 levels of the above risk factors and for prevalence of the above diseases/disorders, accounting for possible confounding by the pre-weight-change levels. The latter levels might have prevailed for a longer period of time and may have carried more significance than levels that accompanied the 1963–1968 weight changes or were provoked by those changes. An alternative analysis adjusted for 1968 levels of the same variables, as well as history of lung disease (the report of dieting was still taken from the 1963 questionnaire, because self-reports on dieting were not sought in 1968). To eliminate a possible effect of preexisting diseases on both weight change and mortality, we repeated all analyses after excluding deaths occurring during the first 5 years of follow-up (1968–1973). Limiting mortality follow-up to 13 years (1973–1986).

For assessment of the effect of weight change on survival, Kaplan-Meier and Cox-adjusted survival estimates for the men, grouped by weight change category, were calculated and plotted with 18-year total mortality taken as the time-dependent event. These survival curves were adjusted for age and the covariates listed above.

RESULTS

Characteristics of men in the five weight change categories

Characteristics of men in the five weight change groups are shown in table 1. Men destined to lose 5 kg or more by 1968 were almost 9 kg heavier in 1963 than those who would increase their weight by at least 5 kg, and the respective mean BMIs were 27.7 and 24.8. By 1968, the "extreme losers," initially representing a group of higher weight than others, had become the leanest group: They had lost 7.6 kg (age-adjusted), on average. Men who subsequently lost at least 5 kg also exhibited considerably higher systolic blood pressures in 1963 than those who gained 5 kg or more (141 mmHg vs. 133 mmHg). The different de-

<table>
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<tr>
<th>Characteristic</th>
<th>Loss of ≥5 kg</th>
<th>Loss of 2–4 kg</th>
<th>Stable within 1 kg</th>
<th>Gain of 2–4 kg</th>
<th>Gain of ≥5 kg</th>
<th>Total</th>
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<tbody>
<tr>
<td>No. of men</td>
<td>633</td>
<td>1,314</td>
<td>2,916</td>
<td>2,706</td>
<td>1,659</td>
<td>9,228</td>
</tr>
<tr>
<td>Age (years) at study entry</td>
<td>51.7 (7.5)*</td>
<td>50.6 (6.8)</td>
<td>49.6 (6.7)</td>
<td>48.6 (6.5)</td>
<td>47.6 (6.4)</td>
<td>49.2 (6.8)</td>
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<td>Body mass index† in 1963</td>
<td>27.7 (3.1)</td>
<td>26.3 (3.2)</td>
<td>25.5 (3.2)</td>
<td>25.2 (3.0)</td>
<td>24.8 (3.1)</td>
<td>25.5 (3.2)</td>
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<td>Body mass index in 1968</td>
<td>25.0 (3.1)</td>
<td>25.3 (3.2)</td>
<td>25.5 (3.2)</td>
<td>26.2 (3.0)</td>
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<td>73.7 (9.9)</td>
<td>71.0 (10.3)</td>
<td>70.1 (10.0)</td>
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<td>Weight in 1968 (kg)</td>
<td>70.5 (9.9)</td>
<td>70.9 (9.9)</td>
<td>71.1 (10.3)</td>
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<td>Systolic blood pressure in 1963 (mmHg)</td>
<td>141 (24)</td>
<td>138 (22)</td>
<td>135 (20)</td>
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<td>Systolic blood pressure in 1968 (mmHg)</td>
<td>139 (24)</td>
<td>139 (24)</td>
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<td>142 (22)</td>
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<td>Diastolic blood pressure in 1963 (mmHg)</td>
<td>87 (12)</td>
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<td>Diastolic blood pressure in 1968 (mmHg)</td>
<td>86 (13)</td>
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<td>87 (12)</td>
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<tr>
<td>Serum total cholesterol in 1963 (mg/dl)‡</td>
<td>214 (43)</td>
<td>213 (40)</td>
<td>211 (40)</td>
<td>208 (39)</td>
<td>204 (39)</td>
<td>209 (40)</td>
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<td>Serum total cholesterol in 1968 (mg/dl)‡</td>
<td>203 (34)</td>
<td>207 (33)</td>
<td>208 (34)</td>
<td>209 (33)</td>
<td>212 (33)</td>
<td>209 (34)</td>
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<td>Smoking in 1963 (%)</td>
<td>49.3</td>
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<td>Diabetes mellitus in 1963 (%)</td>
<td>10.3</td>
<td>6.8</td>
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<td>Diabetes mellitus in 1968 (%)</td>
<td>20.9</td>
<td>11.9</td>
<td>8.4</td>
<td>8.3</td>
<td>7.4</td>
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<td>Medical history in 1968 (%)</td>
<td>11.1</td>
<td>6.5</td>
<td>5.5</td>
<td>4.1</td>
<td>5.1</td>
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<td>Myocardial infarction</td>
<td>1.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
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<td>Cancer</td>
<td>18.7</td>
<td>15.2</td>
<td>13.9</td>
<td>10.2</td>
<td>14.3</td>
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<td>Angina</td>
<td>9.9</td>
<td>5.1</td>
<td>4.2</td>
<td>4.8</td>
<td>3.2</td>
<td>4.6</td>
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* Numbers in parentheses, standard deviation.
† Weight (kg)/height (m)^2.
‡ Data were available only for the 9,094 subjects who had blood drawn for blood chemistry assessment.
Degrees of weight reduction brought about an equality of mean systolic blood pressures in the weight change groups—on the order of 139–140 mmHg—by 1968. The same held true for diastolic blood pressure. No change in mean diastolic blood pressure was observed among the “extreme losers,” whereas among those who gained 5 kg or more, the age-adjusted mean rose from 82 mmHg in 1963 to 88 mmHg in 1968.

By 1968, the balance had shifted for cholesterol precisely as it had for body weight, reversing the order of the mean cholesterol levels in the groups vis-à-vis 1963. The prevalence of diabetes mellitus among the extreme weight losers remained greatly increased by 1968. Among the extreme losers, 20.9 percent were diabetic in 1968, as compared with 8.4 percent in the stable weight group. The prevalence rates for cancer, myocardial infarction, hypertension, and definite angina were all higher, in 1968, among men who had lost weight than among those who had maintained a stable weight. Additional analysis (results not tabulated) indicated that the extreme losers had also incurred the highest incidence of myocardial infarction (8.8 percent), definite angina (7.2 percent), and diabetes (10.0 percent) (rates for all three endpoints were age-adjusted) between 1963 and 1968. The above three rates were notably higher than the corresponding ones in the other weight change groups (p < 0.01 for all comparisons), indicating a greater weight loss and an increasing frequency of becoming sick between 1963 and 1968.

The characteristics of the study participants were also examined by 1963–1968 weight change category for the 2,471 men reported to be dieting in 1963, separately for the 636 who were on a diet “to lose weight” and the 1,835 who were dieting “for health reasons.” The results (not tabulated) indicated few differences in comparison with the change in baseline risk factor levels in the entire study sample. The “slimmers” included fewer cigarette smokers (42.5 percent) than the group that was not dieting (54.3 percent), and, as expected, they were considerably heavier (mean weight = 78.2 kg; mean BMI = 27.8) than the rest of the study sample. Approximately 12.2 percent of the men who reported dieting for health reasons were diabetic, a frequency about five times that seen among the nondieters or those on a slimming diet. Subsequently (1963–1968), approximately 4 percent of the men in each dieting category developed diabetes. Men dieting for health reasons also exhibited about twice the frequency of coronary heart disease. Both dieting groups exhibited considerably higher frequencies of hypertension than counterparts reporting no special diet.

Those dieters who lost more than 5 kg between 1963 and 1968 had entered the study with an average weight of 84.4 kg (declining to 76.9 kg by 1968) and an average BMI of 29.9 in 1963. A portion of those reportedly attempting to lose weight had put on further weight. This is reflected by the fact that the eventual “extreme gainers” among the men hoping to lose weight through dieting reached an average weight of 83.5 kg by 1968. This left them an average of 8 kg heavier than “extreme gainers” among the other study subjects. The blood pressure levels of those attempting to lose weight were somewhat higher than those of the other subjects. We found a difference between the patterns of risk factor change, over 5 years, among the groups by reported diet: Slimmers, those reporting dieting in order to lose weight, increased their mean blood pressures regardless of the extent or direction of their weight change, whereas among those dieting for health reasons, extreme weight loss was accompanied by a small reduction in mean diastolic and systolic blood pressures. No notable differences in the change patterns of other risk factors were seen.

**Mortality**

During the 18-year follow-up period (1968–1986), 2,983 of the 9,228 study subjects (32.3 percent) died. Coronary heart disease was denoted as the underlying cause of death in 942 men (31.6 percent of all deaths occurring during these years). A total of 1,390 men died of cardiovascular disease and 1,593 of all non-cardiovascular diseases. Of the latter men, 621 died of cancer. The 18-year age-adjusted mortality rates per 1,000 person-years in the five initial BMI groups were 16.5, 13.8, 14.9, 16.3, and 20.1, so only men in the top BMI quintile were exposed to significantly increased long term mortality. Age-adjusted mortality rates in the weight change groups declined progressively with increasing weight gain: 20.9, 17.1, 15.3, 14.2, and 14.8 per 1,000 person-years, respectively (figure 1). This analysis was conducted again after exclusion of the first 5 years of follow-up (1968–1973), in order to eliminate a possible effect of preexisting disease. This made no difference in the above pattern; the rates of mortality between 1973 and 1986 were 18.7, 15.2, 13.3, 11.6, and 11.0 per 1,000 person-years in the five weight change groups, respectively. This trend of declining rates persisted for all mortality endpoints.

The relative risk of mortality among the extreme weight losers, pooled over five moving age groups (see “Materials and Methods”), compared with the men who maintained a stable weight, varied as follows: for total mortality, it was 1.36 (95 percent confidence interval (CI) 1.20–1.55); for cardiovascular disease mortality, 1.40 (95 percent CI 1.16–1.69); for all non-cardiovascular disease mortality, 1.33 (95 percent CI 1.11–1.59); for coronary heart disease mortal-
ity, 1.55 (95 percent CI 1.25–1.93); and for cancer mortality, 0.90 (95 percent CI 0.65–1.24).

**Mortality by initial BMI**

Figure 2 presents 18-year total mortality by baseline BMI and weight change group. Increased mortality rates among weight losers were observed in each BMI group. However, the increased risk associated with weight loss was most marked in the “lean losers”: An age-adjusted mortality rate of 31.0 per 1,000 person-years was observed among the leanest men (BMI <22 at baseline) who lost 5 kg or more, as compared with 18.7 in the stable weight group (RR = 1.67, 95 percent CI 0.90–3.09). Men with high initial relative weight (BMI ≥30) who lost 5 kg or more exhibited a considerably reduced excess risk of mortality, the rate being 22.8 per 1,000 person-years as compared with 19.2 in the stable weight group (RR = 1.18, 95 percent CI 0.86–1.62). Relative risks in the three middle BMI groups were intermediate: 1.29 (95 percent CI 0.94–1.76), 1.44 (95 percent CI 1.08–1.93), and 1.42 (95 percent CI 1.13–1.78) for initial BMIs of 22–25, 25–27, and 27–30, respectively. In a separate analysis, rates of mortality in the initial BMI × weight change groups were examined with and without adjustment for the three dieting categories (dieting to lose weight, dieting for health reasons, not dieting). This was done under indirect adjustment, adjusting for exact age only, and in alternative analysis adjusting for both exact age and dieting category. The mortality rates changed very little as a result of the additional adjustment. The patterns described above—i.e., increased mortality being associated in particular with lean individuals who lost further weight—remained unaffected.

The definition of weight change categories in terms of absolute weight reductions or increases can be contested on the grounds that relative weight changes are more significant than absolute ones. We therefore repeated the calculation of age-adjusted all-cause and coronary heart disease mortality rates after defining the groups (in ascending order of weight change) by relative weight change: losers of 7 percent or more, losers of more than 3 percent but less than 7 percent, men with stable weight (those remaining within 3 percent of their 1963 weight), gainers of more than 3 percent but less than 7 percent, and gainers of 7 percent or more. The crude mortality rates (not tabulated) per 1,000 person-years were 25.3, 20.3, 15.7, 13.0, and 12.8 for 1968–1986 mortality and 18.7, 16.5, 13.1, 11.3, and 10.9 for 1973–1986 mortality. When data were stratified by initial BMI, the results (not shown) closely resembled those obtained by the use of absolute weight change as shown in figure 2. For example, among men in the bottom baseline quintile of BMI, age-adjusted mortality rates for 1968–1986 were 28.6 per 1,000 person-years for men losing ≥7 percent of their 1963 weight, 17.0 for men losing 3–7 percent, 18.4 for men with stable weight, 14.6 for gainers of 3–7 percent, and 15.9 for gainers of ≥7 percent. The corresponding rates among men in the five weight change categories defined by absolute weight change (figure 2) were 31.0, 16.8, 18.7, 14.4, and 16.1 per 1,000 person-years. The results for the
four other baseline BMI quintiles also showed remarkable similarity regardless of whether they were obtained using absolute weight change or relative weight change. We concluded that observing mortality in weight change categories defined by relative weight change rather than absolute weight change made a negligible difference.

Analysis in age groups

Analyses were repeated separately for men in the age groups 40–49 years, 50–59 years, and ≥60 years. In the men aged 40–49 years, the mortality rate was 13.0 per 1,000 person-years among extreme losers versus 9.4 per 1,000 in the stable weight group (RR = 1.38); in the age group 50–59 years, mortality was 29.2 per 1,000 person-years in extreme losers versus 21.1 in the stable weight group (RR = 1.55); and in the age group ≥60 years, it was 50.8 per 1,000 versus 42.3 (RR = 1.20).

Mortality by reported diet

Table 2 shows the age-adjusted mortality rates in the five weight change categories for 1) the 1,835 subjects who, in 1963, reported being on a diet for medical reasons; 2) the 636 subjects who reported being on a diet for slimming purposes; and 3) men who were not dieting in 1963. Among the men on a slimming diet, 18-year mortality was 23.5 per 1,000 person-years in extreme weight losers as compared with 12.7 in men who maintained a stable weight. In men not on a diet,
the difference between the corresponding rates (19.9 and 14.9 per 1,000 person-years, respectively) was only half as large.

Multivariate analysis of mortality

Table 3 presents estimated relative risks for all-cause and coronary heart disease mortality associated with either weight loss or weight gain in comparison with the stable weight group, corrected for age and established coronary heart disease risk factors. We conducted this analysis adjusting for risk factors as assessed in 1963, for reasons explained above, as well as a similar analysis adjusting for risk factors as assessed in 1968, at the end of the weight change period. For each cause of death except cancer, a decrease of 5 kg or more was associated with a statistically significant increased adjusted risk. We obtained the following relative mortality risks (adjusted for 1968 levels of risk factors) in men who had lost at least 5 kg of body weight in comparison with counterparts maintaining a stable weight: 1.24 (95 percent CI 1.08–1.42) for all-cause mortality, 1.34 (95 percent CI 1.09–1.64) for cardiovascular mortality, 1.16 (95 percent CI 0.96–1.41) for all noncardiovascular mortality (the latter two not tabulated), and 1.42 (95 percent CI 1.12–1.79) for coronary heart disease mortality. For cancer mortality, the corresponding relative risk was 0.77 (95 percent CI 0.54–1.09).

We repeated a multivariate analysis of all-cause mortality adjusting for self-reported dieting in 1963. All of the relative risks estimated from the previous analysis and the respective ones from an analysis adjusting for diet were nearly identical.

When only mortality between 1973 and 1986 was considered (eliminating the first 5 years of follow-up), the relative risks associated with extreme weight loss declined further to 1.17 (95 percent CI 0.99–1.37) for all-cause mortality and 1.39 (95 percent CI 1.06–1.83) for coronary heart disease mortality (adjusted for risk factors at 1968 levels and comorbidity). The 1973–1986 relative risks of mortality would be further reduced to values only marginally exceeding 1 if they were adjusted for the risk factors defined according to pre-weight-change (1963) levels—that is, 10 years prior to the 1973–1986 follow-up period.

The time pattern of the 18-year total mortality, by weight change category, is shown by Kaplan-Meier survival curves in figure 3. The increased mortality in men who had lost 5 kg or more was augmented over time. Approximately 15 years into the follow-up period, excess mortality became apparent among subjects who had lost 2–4 kg. The covariate-adjusted curves, shown in figure 4, indicate that adjustment for age and other risk factors still placed the extreme weight loss group at increased risk for mortality.

Covariate-adjusted relative risks for total mortality (adjusting for risk factors at 1968 levels and disease prevalence) were also calculated separately for nondieters, all dieters, and slimming dieters. In these three groups, the relative risks were 1.23 (95 percent CI 1.04–1.47), 1.30 (95 percent CI 1.02–1.65), and 1.56 (95 percent CI 0.95–2.57), respectively, among men who had lost more than 5 kg, compared with counterparts maintaining a stable weight. There was considerable overlap between the confidence intervals of these three relative risks.

DISCUSSION

"[T]he necessity of weight reduction as a critical intervention in modifying [coronary disease] risk" was emphasized as late as 1986 (16, p. 416), and men who gained "substantial weight" were assumed to "have changes... that place them at greater risk of cardiovascular disease and thus at greater risk of premature disability and death" (16, p. 418). In departure with what had seemed the conventional wisdom, the observation of actual mortality in other studies (1) and in ours in fact demonstrated that men who lost the most weight (≥5 kg) went on to experience the highest rate of mortality (particularly from coronary heart disease) among the five weight change groups considered. In the present study, men who had gained the most

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<table>
<thead>
<tr>
<th>Weight change (kg) between 1963 and 1968</th>
<th>Adjusting for risk factors as assessed in 1963</th>
<th>Adjusting for risk factors as assessed in 1968</th>
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<tr>
<td></td>
<td>RR† 95% CI</td>
<td>RR† 95% CI</td>
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<tr>
<td>All-cause mortality</td>
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<tr>
<td>Loss, ≥5</td>
<td>1.18 1.03–1.35</td>
<td>1.24 1.08–1.42</td>
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<td>1.06 0.84–1.19</td>
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<td>Gain, 2–4</td>
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<td>Gain, ≥5</td>
<td>0.98 0.88–1.10</td>
<td>0.91 0.80–1.02</td>
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<td>Coronary heart disease mortality</td>
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<td>1.22 0.97–1.53</td>
<td>1.42 1.12–1.79</td>
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<tr>
<td>Stable, ±1</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gain, 2–4</td>
<td>0.86 0.72–1.02</td>
<td>0.84 0.70–1.01</td>
</tr>
<tr>
<td>Gain, ≥5</td>
<td>0.86 0.81–1.22</td>
<td>0.86 0.69–1.06</td>
</tr>
</tbody>
</table>

* Both analyses were adjusted for age, body mass index, systolic blood pressure, serum total cholesterol, smoking, diabetes mellitus, cancer, history of myocardial infarction, definite angina, intermittent claudication, history of chronic lung disease (1968 only), and being on a diet in 1963.
† RR, relative risk; CI, confidence interval.
Weight exhibited a worsened cardiovascular risk profile after 5 years but failed to show any subsequent increase in their mortality from coronary heart disease and all causes.

The patterns of blood pressure and cholesterol change, as well as coronary heart disease and diabetes prevalence, that accompanied different patterns of weight change in our study closely resembled those observed between the fourth and ninth examinations of the Framingham Heart Study (3). Rankings for weight, systolic blood pressure, and serum total cholesterol were reversed between the weight change groups by the end of the weight change period, the men who had lost ≥5 kg having experienced favorable changes in their spectrum of coronary disease risk factors. An increased risk of both cardiovascular and noncardiovascular mortality was associated with weight reduction over 5 years. After correction for age differences, an excess 18-year mortality between 16 percent and 42 percent was associated with a weight reduction of at least 5 kg over 5 years. Non-cardiovascular disease mortality was increased less than cardiovascular disease mortality.

In one study where weight gainers did proceed to experience increased mortality—the 11-year follow up of 11,703 Harvard University alumni aged 35–74 years (17)—the group at greatest risk of all-cause mortality was still those who lost 5 kg or more.

A review by Andres et al. (1) established that in 13 studies, despite diversity of the populations studied, different omissions of clinically ill persons, and differences in analytical methods, adults who had lost weight or had gained an excessive amount of weight were at increased risk of death. It also established that the lowest mortality was generally associated with modest weight gains. Our results agree with most of these conclusions, with the qualification that we did not find increased mortality following weight gain.

Our finding that weight loss was not associated with a subsequent increase in cancer mortality contrasts with the impression once prevailing that weight loss, potentially prompted by latent malignancy, would herald cancer mortality. However, our finding is consistent with the findings for Harvard alumni (17), where cancer mortality was virtually equal in all five weight change categories.
Initial weight appeared to influence the fate of those who lost weight subsequently. We found the strongest association of weight loss with subsequent mortality among individuals who were the leanest at the beginning of the study (BMI <22). Weight loss may affect mortality risk more severely when it occurs in lean persons.

Our study has the partial advantage of having queried men with respect to the diets they were on when they entered the study. In this manner, we were able to analyze the association of weight change with mortality separately for the 2,471 men (one quarter of the study subjects) who reported dieting for any reason. The results for this subset of the study subjects mirror those for the nondieters. Specifically, for the 636 men who had reported that they were dieting for slimming purposes rather than for a specific medical reason, the risk of mortality among the losers of ≥5 kg was nearly double that of the stable group. When dieting men were removed and only the results for men not on a diet were examined, no effect on the overall results was seen. We have no information with respect to diets begun after the initial examination, nor did we follow up on the evolving dietary habits of the participants. Therefore, we cannot divide the follow-up period into distinct voluntary and involuntary weight change periods for each subject. It does appear, however, that the association between weight change and mortality was not restricted to those on a diet.

Past surveys have shown that obese persons probably eat amounts equal to or smaller than those eaten by lean individuals (6, 18). This demonstrates the complexity of understanding obesity. Genetic studies have clarified that major variation in both weight and weight change is controlled by factors which remain to be delineated (19). Remarkable success is sometimes seen in an acute reduction of weight (20), but dieters almost invariably regain their weight. The intricacies of weight loss and its sequelae remain complex.

A limitation of the present study, as well as of similar ones, is that further weight changes taking place during the follow-up period (after 1968) were not known. Weight change over a 5-year period is insufficient to fully characterize weight change over a
lifetime, both prior to middle age and later in life.

In conclusion, the increased mortality found among weightlosers remains an enigma. The current study and other studies indicate that involuntary weight loss might be associated with a small increase in the risk of all-cause mortality. If this increased risk is genuine, it is most hazardous in men who are already lean (BMI < 22). Our results do not permit a definite statement beyond observation of the association. Statistical adjustment, by multivariate analysis, for differences in the levels of prognostic variables may not have sufficed to remove all of the prognostic differences between groups of men who exhibited differing weight change patterns. Therefore, we cannot determine beyond a doubt whether weight loss, at an average annual rate of 1 kg or greater, over a period of 5 years in middle-aged and elderly men has a genuine net adverse effect. The alternative hypothesis is that weight loss accompanies and reflects morbidity in men with a poor prognosis. Our results are also consistent with a possible increase in mortality risk conferred by an attempt to alter weight, in addition to that resulting from more frequent disease among persons attempting it. Being based on observation rather than on randomized intervention designed to examine the safety of weight loss, this hypothesis remains tentative. These results reinforce the need for a better understanding of involuntary weight reduction and a reappraisal of weight reduction as a preventive health measure.

REFERENCES