

## ASSOCIATION OF WEIGHT LOSS AND WEIGHT FLUCTUATION WITH MORTALITY AMONG JAPANESE AMERICAN MEN

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**Abstract** *Background.* Weight loss and fluctuations in weight have been associated with increased risks of death from cardiovascular disease and from all causes. The clinical and public health implications of these associations are unclear.

*Methods.* We examined the long-term relation of weight change and fluctuation in weight with mortality over a 6-year period in 6537 middle-aged Japanese American men enrolled in the Honolulu Heart Program, a prospective study (mean follow-up, 14.5 years).

*Results.* Men who had a weight loss of 4.5 kg or more or who had large fluctuations in weight (or both) over a six-year period were, on average, in poorer health than their peers whose weight was more stable. After the exclusion of subjects who died during the first five years of follow-up and after adjustment for confounding factors, a weight loss of more than 4.5 kg was associated with the risk of death from all causes, with the exception of death from cancer. The subjects whose weight fluctuat-

ed the most had a significantly higher risk of death from cardiovascular causes (relative risk, 1.41; 95 percent confidence interval, 1.03 to 1.93), death from noncardiovascular and noncancerous causes (relative risk, 1.53; 95 percent confidence interval, 1.12 to 2.10), and death from all causes (relative risk, 1.25; 95 percent confidence interval, 1.05 to 1.48). However, the associations of weight loss and variation in weight with death from cardiovascular causes and from noncardiovascular and noncancerous causes were not found among healthy men who had never smoked.

*Conclusions.* The associations between weight loss or fluctuation and mortality were partially explained by confounding factors and by the presence of preexisting disease. However, weight loss and weight fluctuation were unrelated to death among healthy men who had never smoked. Thus, concern about the health hazards of weight loss and variation may not be applicable to otherwise healthy people. (*N Engl J Med* 1995;333:686-92.)

MANY studies have observed a relation between weight loss or variation in weight (fluctuation) and increased mortality from cardiovascular causes and from all causes,<sup>1-12</sup> although this is not a universal finding.<sup>13,14</sup> Whether weight loss or fluctuations have adverse health implications (cause-effect), are consequent to antecedent disease (effect-cause), or are confounded by extraneous factors is not clearly established.<sup>15,16</sup> For example, the relation of low body weight (or recent weight loss) and decreased longevity may be due, at least in part, to a failure to control adequately for cigarette smoking.<sup>17</sup> Since dieting and weight cycling are now very common, a better understanding of their health implications is an important public health priority.<sup>18</sup>

We prospectively examined the relation between weight change and fluctuation and mortality, using data from the Honolulu Heart Program. We addressed two questions: Are the observed associations of weight loss and weight variation with mortality due to effect-cause (underlying disease) or to confounding by other factors? Are these associations confined to men with preexisting disease or to cigarette smokers?

### METHODS

#### Study Population and Procedures

The Honolulu Heart Program is a prospective study of cardiovascular disease among Japanese American men who were 45 to 68

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Supported under contracts (NO1-HC-02901 and NO1-HV-02901) with the National Heart, Lung, and Blood Institute.

years old and living on the island of Oahu, Hawaii, in 1965. The cohort recruitment and study design and procedures have been described elsewhere.<sup>19,20</sup> In brief, a base-line examination of 8006 participants was carried out from 1965 to 1968. Of these, 7498 men (93.6 percent) completed the second examination during 1968 to 1970, and 6860 men (85 percent) were examined a third time in 1971 to 1974. At each examination, information was collected on sociodemographic characteristics, medical history, anthropometric measures, smoking status, alcohol consumption, physical activity, and blood chemistry. Body weight was measured with a balance scale with the subjects in light clothing and without shoes.<sup>21</sup> Body-mass index (the weight in kilograms divided by the square of the height in meters) was calculated. A physical-activity index was calculated as a weighted sum of the number of hours per day subjects spent at each of five levels of activity.<sup>22</sup> Dietary assessment was done by a dietitian using the 24-hour recall method.<sup>23</sup> Alcohol intake, expressed as milliliters of ethanol per day, was estimated on the basis of each subject's usual consumption of beer, wine, and liquor. Beer was considered to be 3.7 percent ethanol; wine, 10 percent; and liquor, 38 percent.<sup>24</sup> Occupations were coded with the 1970 U.S. Census Alphabetical Listings for Industries and Occupations.<sup>25</sup>

For the present analysis, mortality follow-up through hospital surveillance, newspaper obituaries, and state health department records covered a 16-year period beginning in 1973 and continuing through the end of 1988 (mean [ $\pm$ SD] follow-up, 14.5 $\pm$ 3.3 years) and was essentially complete. For each death, an underlying cause was assigned by a medical review panel on the basis of relevant clinical records and coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8). A follow-up survey in 1984 found that only 1.3 percent of the men could not be traced.<sup>26</sup> The exclusion of men with missing data at any examination yielded a sample of 6537 men for multivariate analysis. No a priori exclusions were made because of preexisting medical conditions. Those with missing data for variables other than weight did not differ significantly from the rest of the cohort with respect to weight-related variables.

#### Statistical Analysis

We investigated two aspects of weight change in relation to mortality. The first was the slope of weight against time derived from the three weight measurements in each man. The slope of weight is an indication of a systematic increase (weight gain) or decrease (weight loss) and is typically related to the initial weight. This correlation be-

tween slope and base-line weight ( $r = -0.16$ ,  $P < 0.001$ ) indicates that heavy men were, on average, more likely to lose weight. This may be due to intentional weight loss or regression toward the mean. On the other hand, the slope was not correlated with the weight averaged over a period of six years ( $r = 0.01$ ,  $P = 0.53$ ). The second index was the root-mean-square error for each subject after removal of the linear change. The root-mean-square error represents the residual variability around the overall time trend of weight (in other words, the within-person weight fluctuation or cycling around the trend in weight).<sup>27</sup>

These two indexes of weight change were used in two ways: as continuous variables to ascertain linear or curvilinear trends in mortality risk and as categorical variables to test hazard ratios for mortality at specific levels of weight change and weight variation.

For weight change, five arbitrary groups were created on the basis of four cutoff points:  $-4.5$ ,  $-2.5$ ,  $+2.5$ , and  $+4.5$  kg. Thus, the five weight-change groups were as follows: weight loss of more than 4.5 kg, weight loss of 2.6 to 4.5 kg, weight loss of 2.5 to weight gain of 2.4 kg, weight gain of 2.5 to 4.5 kg, and weight gain of more than 4.5 kg. The middle group ( $-2.5$  to  $+2.4$  kg) was chosen as the reference group (e.g., risk = 1). These groups represented 12, 14, 57, 10, and 7 percent of the cohort, respectively. For the root-mean-square error, five groups were defined on the basis of quintiles of the distribution of the root-mean-square error in men free of disease.

To estimate the age-adjusted risk of cause-specific death as a function of weight change and weight variation (as both continuous and categorical variables), we used the Cox proportional-hazards model.<sup>28,29</sup> We then examined multivariate models including dummy variables for smoking status (those who had quit smoking before the first examination, those who continued to smoke, and those who quit smoking between examinations 1 and 3 as compared with those who had never smoked), base-line alcohol consumption (abstainers and heavy drinkers [ $>40$  ml of ethanol per day, the upper quintile among drinkers] as compared with light or moderate drinkers), and job (blue collar and white collar), plus continuous variables for the intensity of smoking (expressed as the number of cigarettes smoked per day), the level of physical activity (in metabolic equivalents), and total energy intake (in calories).

The principal outcomes were as follows: death from all cardiovascular causes ( $n = 355$ ), which was further subdivided into death from coronary heart disease ( $n = 186$ ) or other circulatory problems ( $n = 169$ ); death from cancer ( $n = 480$ ); death from noncardiovascular and noncancerous causes ( $n = 382$ ); and death from all causes ( $n = 1217$ ). The end point of death from noncardiovascular and noncancerous causes encompassed respiratory ( $n = 82$ ), digestive ( $n = 14$ ), liver ( $n = 21$ ), renal ( $n = 8$ ), neurologic ( $n = 14$ ), infectious ( $n = 12$ ), and traumatic ( $n = 39$ ) causes of death and those not elsewhere classified or deaths whose cause was unknown ( $n = 192$ ).

To assess the full effect of weight indexes on mortality, we made no attempt to control for intermediate variables such as serum cholesterol concentrations, blood-pressure levels, and blood glucose concentrations.

To compensate for bias caused by latent disease leading to weight change and premature death, we analyzed the data after excluding those for years 1 through 5 of follow-up. To account for the confounding effect of preexisting disease on weight-mortality associations, a two-level variable (equal to 1 if at least one health condition was present, and 0 otherwise) was also added as a covariate. The following non-mutually exclusive medical conditions were identified: coronary heart disease ( $n = 731$ ), cerebrovascular disease ( $n = 177$ ), cancer ( $n = 191$ ), thyroid disease ( $n = 91$ ), diabetes mellitus ( $n = 1185$ ), hypertensive disease ( $n = 2106$ ), benign gastrointestinal tumors ( $n = 106$ ), partial or total gastrectomy ( $n = 299$ ), colectomy ( $n = 65$ ), diverticulitis ( $n = 82$ ), peptic ulcer disease ( $n = 696$ ), cirrhosis of the liver ( $n = 21$ ), lung disease ( $n = 523$ ), gout ( $n = 585$ ), and miscellaneous conditions ( $n = 324$ ). The miscellaneous subgrouping included a history of rheumatic fever and use of anticoagulants, corticosteroids, or anticonvulsants. Criteria for inclusion as a preexisting health condition included a definite discharge diagnosis, existence of surgical reports, or documented prescription of drugs or diets for hypertension or diabetes.

To address whether the relation between a change or variation in body weight and mortality was homogeneous in the study population,

we calculated the relative risk after stratifying the cohort according to smoking and disease status. A two-tailed  $P$  value of 0.05 was considered to indicate statistical significance.

## RESULTS

### Association between Body-Mass Index and Mortality

Although the focus of the analysis was on weight change and variation in weight, the primary association between weight and mortality is relevant to the interpretation of our data. Thus, adjusted mortality rates, according to quintiles of average body-mass index over a six-year period (1965 through 1971) and smoking status, are shown in Figure 1. Mortality was elevated at both low and high body-mass indexes in men with evidence of disease, most clearly among those who were current smokers and those who had never smoked (Fig. 1, top panel). In men who were free of disease and who either had never smoked or had stopped smoking, mortality generally increased with increasing body-mass index, although the rate in the first quintile was slightly higher than the rate in the second quintile, creating a shallow  $J$ -shaped pattern (Fig. 1, bottom panel). In current smokers free of documented disease, body-mass index had no clear relation to mortality.

### Correlates of Linear Weight Change

Men who lost more than 4.5 kg during the six-year period tended to be older and heavier at the base-line examination (Table 1). In addition, they were more likely to be heavy drinkers who continued to smoke, with a higher prevalence of most diseases, notably coronary heart disease, diabetes mellitus, and hypertensive disease. Men who lost weight also had a lower caloric intake and lower physical-activity index than men whose weight was stable or who gained weight. In turn, participants gaining more than 4.5 kg were more likely to have quit smoking and to have blue-collar jobs (Table 1).

### Correlates of Weight Variation

Subjects whose weight fluctuated the most were heavier at base line and were more likely to be heavy drinkers and to have quit smoking between examinations (Table 2). These subjects also had a higher prevalence of most diseases.

### Survival Analysis of Weight Change Adjusted for Weight at Base Line

Adjusted relative risks of all mortality outcomes, with the exception of cancer, increased in a steady fashion from weight gain to weight loss (Table 3). Men losing more than 4.5 kg had, independently of the level of weight at base line and confounders, a significantly elevated risk of death from noncardiovascular and noncancerous causes and from all causes. A weight loss of at least 4.5 kg was significantly associated with death from coronary and cardiovascular disease in the age-adjusted models, but this association was somewhat diminished and became nonsignificant when other risk factors were considered. After adjustment for con-

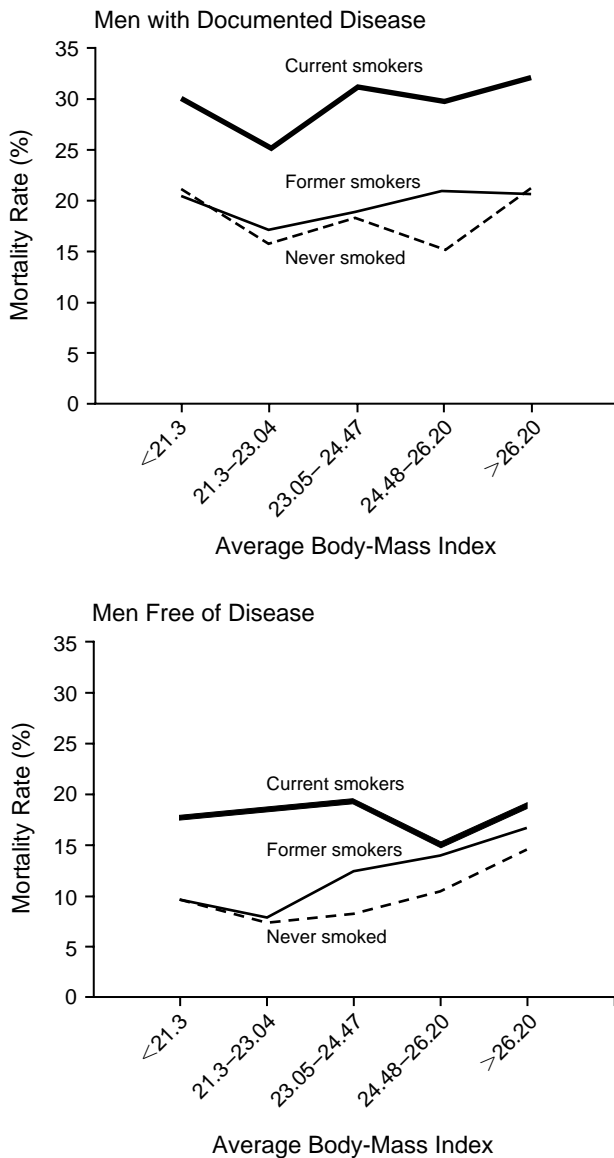


Figure 1. Adjusted Mortality Rates during 16 Years of Follow-up, According to Average Body-Mass Index, Prevalence of Documented Disease, and Smoking Status at the Base-Line Examination.

founders and prevalent disease, a weight loss of 2.6 to 4.5 kg was related to death due to other circulatory diseases, noncardiovascular and noncancerous causes, and all causes. A weight gain of 4.5 kg, as compared with a minimal change in weight (−2.5 to +2.5 kg), was not significantly related to any cause of death (Table 3). Men who gained moderate amounts of weight (+2.5 to +4.5 kg) were at the lowest risk of dying.

#### Survival Analysis of Weight Variation Adjusted for Trend and for Weight at Base Line

Men with the greatest variation in weight were at higher risk of death from coronary heart disease, all cardiovascular diseases, noncardiovascular and non-

cancerous causes, and all causes. The magnitude of the risk was only marginally attenuated in multivariate analysis (Table 4). The risk of death from cancer was unrelated to the root-mean-square error of weight.

#### Analysis Stratified According to Disease and Smoking Status

Since both weight loss and weight variation were related to smoking status and disease status, we performed additional analyses stratifying the cohort into four mutually exclusive groups according to disease and smoking status. Approximately 12 percent of the participants (n = 790) had never smoked and were free of documented disease (Table 5).

The association of weight loss with death from noncardiovascular and noncancerous causes and from all causes was most accentuated in smokers without disease and in those with disease who had never smoked. On the other hand, weight loss did not have a significant association with mortality in men who were free of disease who had quit smoking or who had never smoked.

The association of weight variation with long-term mortality was also nonuniform across the study population. For instance, the strongest association between the top quintile of weight variation and death from cardiovascular disease was observed among smokers with existing disease. Conversely, large variations in weight were unrelated to death from cardiovascular disease among healthy men who had never smoked. Similarly, large weight variations were a statistically significant risk factor for death from noncardiovascular and noncancerous causes and from all causes in smokers who were free of disease and were a nonsignificant factor among those free of disease who had never smoked.

#### DISCUSSION

This study has four main findings. First, weight loss and weight variation were not significantly related to mortality in healthy men who had never smoked. Conversely, weight loss and weight variation were associated with mortality in men with a preexisting health condition, current smokers, and men with both adverse characteristics. Second, weight loss, independently of the level of weight at base line, was associated in the long term with all mortality outcomes except death from cancer. Most associations weakened when the analysis was adjusted for confounders, including preexisting disease. Third, large variations in weight, independently of level and trend of weight, were predictive in the long term of death from cardiovascular disease, noncardiovascular and noncancerous causes, and all causes. These risk relations were only partially accounted for by confounding and existing disease. Fourth, the association of a low average body-mass index with overall mortality was more pronounced in men with documented disease.

There is almost certainly residual confounding in the analysis that controlled for preexisting disease and

Table 1. Distribution of Health-Related Variables According to Change in Weight over a Six-Year Period.

VARIABLE	CHANGE IN WEIGHT*				
	LOSS OF >4.5 kg (N = 774, 11.8%)	LOSS OF 2.6 TO 4.5 kg (N = 928, 14.2%)	LOSS OF 2.5 kg TO GAIN OF 2.4 kg (N = 3735, 57.1%)	GAIN OF 2.5 TO 4.5 kg (N = 669, 10.2%)	GAIN OF >4.5 kg (N = 431, 6.6%)
Age (yr)	54.6±5.5	54.2±5.4	53.9±5.4	53.7±5.3	53.7±5.5
Base-line body-mass index	25.2±3.0	24.3±3.0	23.6±2.9	23.6±2.9	23.2±3.1
Base-line weight (kg)	67.8±9.6	64.7±9.3	62.5±9.0	63.2±9.1	62.6±9.7
Mean weight (kg)†	64.8±9.3	63.2±9.2	62.4±9.0	64.7±9.1	65.6±9.6
Root-mean-square error‡	9.5±68.4	3.4±7.0	2.7±8.6	3.9±19.7	10.4±37.5
Nondrinker (%)	38.1	38.4	35.8	37.8	34.6
Heavy drinker (%)§	14.5	11.9	10.5	10.3	11.4
Alcohol consumption (ml/day)¶	23.3±27.6	22.3±27.0	19.7±24.9	19.8±22.7	22.8±31.1
No. of subjects	479	572	2399	416	282
Physical-activity index (metabolic equivalents)	32.1±4.3	32.2±4.1	33.0±4.6	33.0±4.5	32.8±4.6
Total calorie intake (kcal)	22.4±7.3	22.9±7.4	23.1±7.1	23.4±7.3	23.5±8.1
Blue-collar job (%)**	90.3	90.0	91.4	89.8	92.8
Never smoked (%)	27.5	32.1	31.0	24.5	18.1
Former smoker (%)	25.8	26.8	25.6	24.1	24.4
Continuing smoker (%)	38.9	34.2	34.1	19.3	29.0
Smoker who quit between examinations 1 and 3 (%)	7.6	6.6	9.1	11.7	28.5
Any preexisting disease (%)	73.9	69.5	58.1	61.4	60.3

\*The change in weight was measured in examinations 1, 2, and 3. The entries for continuous variables are means ±SD.

†Mean weight at examinations 1, 2, and 3.

‡Root-mean-square error from the regression of weight on time since the first examination.

§Those who drank >40 ml of ethanol per day (upper quintile among drinkers).

¶Among those who drank any amount of alcohol.

||On the basis of 24-hour dietary recall.

\*\*Farmers, laborers, craftspeople, service workers, and operatives.

smoking, because a large number of diseases with variable degrees of severity were considered together, and the measurement of both smoking status and intensity of smoking may be erroneous. Other sources of residual confounding are unmeasured environmental, health, or genetic factors. Thus, the association of weight loss and weight variation with mortality most likely reflects bias or artifact. An alternative interpretation, however,

is that weight loss or weight cycling may be deleterious in unhealthy people and in smokers.

Death from coronary heart disease and cardiovascular disease was associated with large variations in weight, a finding consistent with those of the Framingham Study<sup>5</sup> and the Multiple Risk Factor Intervention Trial.<sup>10</sup> However, these studies, unlike the Honolulu Heart Program, were not able to separate out men with

Table 2. Distribution of Health-Related Variables According to Quintiles of Weight Variation.

VARIABLE	QUINTILE OF WEIGHT VARIATION*				
	1 LEAST VARIATION (N = 1202, 18.4%)	2 (N = 1258, 19.2%)	3 (N = 1219, 18.6%)	4 (N = 1295, 19.8%)	5 MOST VARIATION (N = 1563, 23.9%)
Age (yr)	53.8±5.4	53.8±5.3	54.2±5.5	54.2±5.5	53.9±5.3
Base-line body-mass index	23.4±2.9	23.6±2.9	23.7±3.0	23.9±2.9	24.4±3.1
Base-line weight (kg)	62.4±9.3	62.5±9.2	62.8±9.2	63.7±9.0	65.9±9.6
Mean weight (kg)†	62.2±9.3	62.3±9.2	62.6±9.1	63.5±8.8	65.2±9.2
Root-mean-square error‡	0.03±0.03	0.31±0.13	0.98±0.27	2.44±0.67	14.7±54.4
Nondrinker (%)	35.3	37.0	37.2	37.2	36.1
Heavy drinker (%)§	9.7	11.1	11.1	10.7	13.1
Alcohol consumption (ml/day)¶	19.1±24.8	20.4±24.4	20.7±26.3	20.1±24.5	22.6±28.1
No. of subjects	778	793	766	813	998
Physical-activity index (metabolic equivalents)	32.8±4.5	32.6±4.4	32.8±4.4	32.7±4.5	32.8±4.8
Total calorie intake (kcal)	23.1±7.1	23.1±7.0	22.8±7.3	23.0±7.1	23.1±7.5
Blue-collar job (%)**	91.0	92.1	91.3	90.3	90.5
Never smoked (%)	30.9	30.4	29.5	30.0	26.0
Former smoker (%)	23.8	26.9	25.8	25.7	25.5
Continuing smoker (%)	35.4	34.0	34.8	32.4	34.1
Smoker who quit between examinations 1 and 3 (%)	9.7	8.2	9.8	11.7	14.1
Any preexisting disease (%)	58.8	60.5	59.3	61.7	68.3

\*The quintiles of root-mean-square errors from the regression of weight on time. The entries for continuous variables are means ±SD.

†Mean weight at examinations 1, 2, and 3.

‡Root-mean-square error from the regression of weight on time since the first examination.

§Those who drank >40 ml of ethanol per day (upper quintile among drinkers).

¶Among those who drank any amount of alcohol.

||On the basis of 24-hour dietary recall.

\*\*Farmers, laborers, craftspeople, service workers, and operatives.

Table 3. Adjusted Risk of Death in Years 6 through 16 of Follow-up, According to Change in Weight.\*

CAUSE OF DEATH (ICD-8 CODE)	NO. OF DEATHS	CHANGE IN WEIGHT†				LINEAR TREND‡	QUADRATIC TREND§
		LOSS OF >4.5 kg	LOSS OF 2.6 TO 4.5 kg	GAIN OF 2.5 TO 4.5 kg	GAIN OF >4.5 kg		
<i>relative risk (95% CI)</i>							
Coronary heart disease (410–414)	186	1.41 (0.95–2.09)	0.93 (0.60–1.44)	0.49 (0.25–0.95)	0.88 (0.49–1.58)	0.05	0.42
Other circulatory causes (393–409, 415–458)	169	1.19 (0.75–1.90)	1.52 (1.00–2.29)	0.81 (0.45–1.47)	1.26 (0.70–2.26)	0.13	0.64
All cardiovascular causes (393–458)	355	1.31 (0.97–1.77)	1.18 (0.88–1.60)	0.64 (0.41–0.98)	1.05 (0.69–1.58)	0.01	0.32
Cancer (141–207)	480	0.93 (0.69–1.26)	1.21 (0.93–1.56)	0.91 (0.66–1.26)	1.07 (0.75–1.52)	0.84	0.68
Noncardiovascular, non-cancerous causes	382	1.45 (1.08–1.94)	1.50 (1.14–1.97)	0.89 (0.60–1.32)	0.82 (0.50–1.32)	0.001	0.81
All causes	1217	1.21 (1.02–1.43)	1.29 (1.10–1.51)	0.83 (0.66–1.02)	0.99 (0.79–1.26)	0.003	0.46

\*Values are the relative risks in relation to the group with a weight change ranging from  $-2.5$  to  $+2.4$  kg, adjusted for age, average weight, smoking status, number of cigarettes smoked per day, base-line alcohol consumption (abstinence, heavy), level of physical activity, total caloric intake, job (blue collar, white collar), and preexisting disease. CI denotes confidence interval.

†Six-year linear change in weight as measured at examinations 1, 2, and 3.

‡Linear term only.

§Linear and quadratic terms.

preexisting major diseases or a history of such conditions and did not examine healthy, nonsmoking persons separately.

Death from cancer was unrelated to weight loss when early deaths were eliminated. However, there was a strong relation between weight loss and fatal cancer in the early follow-up period (data not shown). This finding is consistent with the effect–cause hypothesis that malignant disease lowers body weight.

Observational studies of free-living populations are vexed by the problem of how to account for the presence of preexisting illness at the time of weight measurement. To deal with this problem, we obtained detailed information on preexisting and previous major medical conditions among the study participants and eliminated data on subjects who died early. Second, we did not adjust for variables in the causal pathway linking body weight and mortality (e.g., serum cholesterol, blood pressure, or blood glucose), because statistical overadjustment may lead to misinterpretation.<sup>17</sup> Third, we used an approach based on the linear slope and the root-mean-square error around the overall trend of

weight over a six-year period. The slope of weight against time reflects linear change, or weight change at a constant or consistent rate. The root-mean-square error (adjusted for the average and the linear slope of weight) captures the component of variation in weight that is inconsistent or not linear (the asymmetric fluctuations in weight, or weight cycling) and that is independent of the level and trend.<sup>30,31</sup> The root-mean-square error is a more sensitive index of weight variation than the coefficient of variation (standard deviation  $\div$  mean), because the coefficient of variation is correlated with the slope ( $r = -0.18$ ,  $P < 0.001$ ). Thus, the coefficient of variation and the slope are collinear, and it is impossible to separate out the trend from asymmetric fluctuation when the coefficient of variation is used as the index of weight variation. On the other hand, the root-mean-square error is independent of the slope ( $r = -0.01$ ,  $P = 0.13$ ).

Definitive interpretation of epidemiologic data on the effects of weight change and weight variation on mortality has been difficult because of lack of biologic plausibility. The authors of early studies in animals conclud-

Table 4. Adjusted Risk of Death in Years 6 through 16 of Follow-up, According to Quintiles of Weight Variation.\*

CAUSE OF DEATH (ICD-8 CODE)	NO. OF DEATHS	QUINTILE OF WEIGHT VARIATION†				LINEAR TREND‡	QUADRATIC TREND§
		2	3	4	5 MOST VARIATION		
<i>relative risk (95% CI)</i>							
Coronary heart disease (410–414)	186	0.98 (0.59–1.62)	1.02 (0.63–1.64)	1.26 (0.80–1.98)	1.29 (0.83–2.01)	0.66	0.21
Other circulatory causes (393–409, 415–458)	169	0.99 (0.59–1.67)	1.17 (0.72–1.90)	0.95 (0.57–1.56)	1.56 (0.99–2.45)	0.76	0.22
All cardiovascular causes (393–458)	355	0.99 (0.69–1.42)	1.08 (0.77–1.52)	1.11 (0.79–1.55)	1.41 (1.03–1.93)	0.60	0.06
Cancer (141–207)	480	1.10 (0.83–1.46)	0.96 (0.72–1.27)	0.91 (0.69–1.21)	0.97 (0.73–1.27)	0.39	0.04
Noncardiovascular, non-cancerous causes	382	1.35 (0.97–1.89)	1.25 (0.90–1.73)	1.08 (0.77–1.52)	1.53 (1.12–2.10)	0.53	0.21
All causes	1217	1.14 (0.95–1.37)	1.07 (0.89–1.29)	1.01 (0.84–1.21)	1.25 (1.05–1.48)	0.27	0.18

\*Values are the relative risks in relation to the group with a weight change ranging from  $-2.5$  to  $+2.4$  kg, adjusted for age, average weight, slope of weight, smoking status, number of cigarettes smoked per day, base-line alcohol consumption (abstinence, heavy), level of physical activity, total caloric intake, job (blue collar, white collar), and preexisting disease. CI denotes confidence interval.

†Quintiles of root-mean-square error from the regression of weight on time.

‡Linear term only.

§Linear and quadratic terms.

Table 5. Adjusted Risk of Death in Years 6 through 16 of Follow-up Associated with Weight Loss of More than 4.5 kg or of 2.6 to 4.5 kg and the Top Quintile of Weight Variation, According to Smoking and Disease Status.\*

SMOKING STATUS	DISEASE STATUS	NO. OF SUBJECTS (%)	NO. OF DEATHS	WEIGHT LOSS†		TOP QUINTILE OF RMSE‡
				>4.5 kg	2.6 TO 4.5 kg	
			ALL CARDIOVASCULAR CAUSES	relative risk (95% CI)		
Current	Preexisting disease	1771 (27.1)	159	1.33 (0.64–2.77)	1.01 (0.58–1.77)	1.93 (1.18–3.17)
	No preexisting disease	1142 (17.5)	34	2.37 (0.26–2.15)	2.80 (0.68–11.3)	1.60 (0.55–4.68)
Former	Preexisting disease	1031 (15.8)	61	0.41 (0.09–1.84)	1.02 (0.42–2.47)	1.32 (0.58–3.01)
	No preexisting disease	621 (9.5)	14	0.50 (0.01–22.9)	0.55 (0.07–4.17)	1.29 (0.60–2.79)
Never	Preexisting disease	1182 (18.1)	67	1.61 (0.45–5.73)	0.96 (0.39–2.33)	1.29 (0.60–2.79)
	No preexisting disease	790 (12.1)	20	0.40 (0.01–9.72)	0.95 (0.12–7.38)	0.88 (0.23–3.30)
			CANCER			
Current	Preexisting disease		196	1.23 (0.55–2.73)	1.62 (0.97–2.68)	0.74 (0.48–1.14)
	No preexisting disease		101	0.42 (0.11–1.63)	0.61 (0.25–1.46)	1.57 (0.83–2.95)
Former	Preexisting disease		55	0.53 (0.11–2.52)	0.78 (0.28–2.18)	1.45 (0.60–3.51)
	No preexisting disease		29	1.90 (0.32–11.2)	1.42 (0.32–6.19)	0.66 (0.16–2.60)
Never	Preexisting disease		69	2.55 (0.73–8.88)	2.23 (1.00–5.00)	0.76 (0.38–1.54)
	No preexisting disease		30	1.71 (0.17–16.4)	1.30 (0.28–5.96)	1.21 (0.35–4.13)
			NONCARDIOVASCULAR, NONCANCEROUS			
Current	Preexisting disease		135	0.94 (0.39–2.22)	1.31 (0.75–2.32)	1.43 (0.85–2.41)
	No preexisting disease		57	5.20 (1.24–21.6)	1.52 (0.48–4.83)	3.94 (1.59–9.74)
Former	Preexisting disease		74	1.68 (0.44–6.41)	1.69 (0.72–3.95)	0.84 (0.40–1.79)
	No preexisting disease		27	1.96 (0.31–12.4)	0.27 (0.03–2.42)	0.63 (0.16–2.44)
Never	Preexisting disease		65	2.35 (0.62–8.84)	2.10 (0.90–4.91)	2.06 (0.93–4.56)
	No preexisting disease		24	0.74 (0.05–9.98)	1.98 (0.47–8.35)	1.37 (0.36–4.81)
			ALL CAUSES			
Current	Preexisting disease		490	1.19 (0.76–1.88)	1.32 (0.97–1.80)	1.22 (0.93–1.60)
	No preexisting disease		192	1.43 (0.60–3.41)	1.08 (0.58–1.99)	2.07 (1.30–3.27)
Former	Preexisting disease		190	0.74 (0.32–1.68)	1.14 (0.68–1.90)	1.17 (0.73–1.87)
	No preexisting disease		70	1.67 (0.51–5.45)	0.71 (0.27–1.88)	0.66 (0.29–1.47)
Never	Preexisting disease		201	2.13 (1.02–4.46)	1.65 (1.02–2.68)	1.21 (0.79–1.86)
	No preexisting disease		74	0.95 (0.21–4.22)	1.40 (0.56–3.51)	1.08 (0.51–2.27)

\*All models are adjusted for age, base-line alcohol consumption (abstinence, heavy), physical activity, total caloric intake, and job (blue collar, white collar). Models for weight change are adjusted for the level of weight; models for weight variability are adjusted for the level and trend of weight. CI denotes confidence interval, and RMSE root-mean-square error.

†Relative risk as compared with the risk associated with a weight change ranging from –2.5 to +2.4 kg.

‡Relative risk as compared with the risk for the lowest quintile of weight variability (root-mean-square error).

ed that repeated episodes of weight loss and gain may alter metabolism and body composition in such a way that future weight loss is jeopardized, thereby promoting obesity.<sup>32</sup> However, this view was challenged by subsequent experiments showing that weight cycling did not increase adiposity, subsequent caloric intake, insulin resistance, blood pressure, or serum cholesterol in rodents.<sup>33–36</sup> In addition, studies examining this paradigm in humans generally do not support the existence of a high prevalence of unfavorable distribution of body fat or unfavorable resting metabolic rate among weight cyclers,<sup>37</sup> or the possibility that a history of weight cycling worsens cardiovascular risk factors.<sup>37–39</sup> Whether weight cycling has negative psychological consequences has received little attention.<sup>40</sup>

A major limitation of this study was the inability to distinguish intentional from unintentional weight loss. However, we compensated for this deficiency by an effort to identify preexisting conditions that could cause involuntary weight loss. Other weaknesses were the use of only three data points to estimate both slope and variation and the inclusion of a relatively small

number of men (and thus deaths among them) who were nonsmokers and initially healthy. As a consequence, the 95 percent confidence intervals for weight change and weight variation in these groups of men were fairly wide. Finally, this is a rather unusual population in that these Japanese American men in Hawaii are notably thinner than whites in the continental United States.<sup>41</sup>

In conclusion, the long-term associations between weight change or weight variation (fluctuation) and subsequent mortality in the men enrolled in the Honolulu Heart Program are only partially attributable to measured confounding factors and to effect–cause (manifest disease). In addition, these associations were modified by the presence of disease and smoking behavior, implying that weight loss (presumably involuntary), weight cycling, or both may reflect ill health but do not appear to be harmful in otherwise healthy persons. Further research is warranted on the effects of multiple cycles of weight loss and gain and on the determinants and consequences of weight fluctuations in persons with diseases and in cigarette smokers.

We are indebted to Peter Hannan, M.S., for his advice on statistical methods and excellent editorial assistance and to Simone French, Ph.D., for her encouragement and helpful suggestions.

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