

The Obesity Paradox and Weight Loss

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ABSTRACT

BACKGROUND: An “obesity paradox,” in which overweight and obese individuals with established cardiovascular disease have a better prognosis than normal weight subjects, has been reported in a number of clinical cohorts, but little is known about the effects of *weight loss* on the obesity paradox and its association with health outcomes.

METHODS: Weight was determined in 3834 men at the time of a clinically referred exercise test and again during a clinical evaluation a mean of 7 years later. The associations among weight changes, baseline fitness, and other risk markers with cardiovascular and all-cause mortality were determined by Cox proportional hazards analysis.

RESULTS: During the follow-up period, 314 subjects died (72 of cardiovascular causes). In a multivariate analysis (including baseline weight, weight change, exercise capacity, and cardiovascular disease), weight gain was associated with lower mortality and weight loss was associated with higher mortality (4% higher per pound lost per year, $P < .001$) compared with stable weight. For all-cause mortality, the relative risks for the no change, weight gain, and weight loss groups were 1.0 (referent), 0.64 (95% confidence interval, 0.50-0.83), and 1.49 (95% confidence interval, 1.17-1.89), respectively ($P < .001$). Those who died and exhibited weight loss had a significantly higher prevalence of deaths due to cancer and cardiovascular causes.

CONCLUSION: Weight loss was related to higher mortality and weight gain was related to lower mortality when compared with stable weight. The obesity paradox in our sample is explained in part by a combination of non-volitional weight loss related to occult disease and a protective effect of weight gain. *Published by Elsevier Inc. • The American Journal of Medicine (2011) xx, xxx*

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The prevalence of obesity has increased dramatically over the last 2 decades and has reached global epidemic proportions in both adults and children in the United States.^{1,2} It is associated with numerous comorbidities, including hypertension, type 2 diabetes, dyslipidemia, and cardiovascular disease.¹⁻³ Obesity is considered 1 of the 5 major risk factors for cardiovascular disease by the American Heart Association and has been shown to be associated with the

development of heart failure, coronary heart disease, sudden cardiac death, atrial fibrillation, and reduced overall survival.¹⁻³ Despite the associations between obesity and these health conditions, a number of recent studies have documented a puzzling phenomenon, termed the “obesity paradox,” in which overweight and obese individuals with established cardiovascular disease have a better prognosis compared with normal weight subjects.^{2,4,5} Other recent studies have explored the role of fitness in the context of the obesity paradox and health outcomes. It has been demonstrated that irrespective of the presence of an obesity paradox or related risk markers, individuals who are relatively fit have significantly better survival and fewer cardiovascular events than unfit individuals.⁶⁻⁸

Although weight reduction is associated with a lessening of hypertension, diabetes, and other cardiometabolic risk markers,^{2,9} there is controversy regarding whether weight

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loss decreases or increases mortality risk.¹⁰⁻¹² Several recent observational studies have reported higher mortality risk with increased weight loss.¹³⁻¹⁵ No doubt this issue is made more complex by the many comorbidities associated with obesity and *non-volitional* weight loss. Variations in preexisting conditions, subclinical disease, smoking, differences in the type of fat loss or fat distribution (eg, visceral fat vs lean mass), and the definition and measure used to classify obesity have been suggested to explain the inconsistent findings on weight loss and mortality.^{2,16} We recently reported the existence of an obesity paradox in our population of veterans who were referred for exercise testing for clinical reasons.^{6,7,17} We observed that exercise capacity strongly affects the obesity paradox; in fact, when stratified by fitness level, the paradoxical association between obesity and mortality was not found in the group registering high fitness.^{7,8} Stated differently, survival was influenced more by exercise capacity than body mass index. Given this finding and the controversial results of previous studies on the effects of weight loss on survival, it would be informative to document the effects of serial changes in both fitness and weight. In the current study, we assessed cardiovascular and all-cause mortality in a subgroup of patients in the Veterans Exercise Testing Study (VETS) who had weights recorded on 2 clinic visits before and after a treadmill test, a mean of 7 years apart. Our objectives were to determine the influence of fitness and *changes* in weight on cardiovascular and all-cause mortality and the extent to which changes in weight could explain the obesity paradox.

MATERIALS AND METHODS

The VETS cohort is an ongoing, prospective evaluation of veteran subjects referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. From the VETS cohort, a list of approximately 10,000 male veterans who had undergone a maximal treadmill test for clinical reasons at the Veterans' Administration (VA) Palo Alto Health Care System between 1992 and 2008 for clinical indications was formed. This list was used to query the VA computerized database to identify patients with weights entered from clinic visits before and after an exercise test. The records were scanned to exclude patients with weight intervals less than 3 months apart, and those who died were reviewed to obtain a final weight that did not reflect a sudden decrease associated with the terminal event. Seven

subjects were excluded because of gastric bypass surgery during the follow-up period. The final sample included 3834 subjects.

Weight change was classified as those whose weight remained stable, those whose weight increased, and those who lost weight between the initial and the subsequent clinic visit. Delta weight was calculated and divided by the time between weights to provide a change per year. Similar calculations were performed to express weight change as a percentage of baseline weight. An alteration in weight (increase or decrease) ≥ 1.0 lb was considered a change. The analyses were repeated using a ≥ 2.0 -lb weight change to determine whether a higher threshold had an appreciable effect on the results. Historical information that was recorded at the time of the exercise test included previous myocardial infarction by history or Q wave, cardiac procedures, heart failure, hypertension, hypercholesterolemia (>220 mg/dL), claudication, chronic obstructive pulmonary disease, cancer, renal disease, diabetes, stroke, smoking status (current, past), and use of cardiac medications.

Exercise Testing

Patients underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol.¹⁸ Standard criteria for termination were used, including moderately severe angina, >2.0 mm abnormal ST depression, a sustained decrease in systolic blood pressure, or serious rhythm disturbances. The Borg 6-20 perceived exertion scale was used to quantify degree of effort.¹⁹ Blood pressure was taken manually, and exercise capacity (in metabolic equivalents [METs]) was estimated from peak treadmill speed and grade.²⁰

No test was classified as indeterminate, medications were not withheld, and age-predicted maximal target heart rates were not used as end points. The exercise tests were performed, analyzed, and reported using a standard protocol incorporating a computerized database with all definitions and measurements prospectively defined.²¹

Outcomes

The main outcome variable was all-cause mortality; cardiovascular deaths and other specific causes of death also were recorded. The California Health Department Service and Social Security Death Indices were used to ascertain the vital status of each patient as of December 31, 2008. Accuracy of deaths was reviewed by 2 clinicians blinded to

CLINICAL SIGNIFICANCE

- Paradoxically, weight loss was related to higher mortality and weight gain was related to lower mortality when compared with stable weight over 7 years. Approximately 60% of the deaths in the weight loss group were attributable to conditions associated with muscle wasting.
- The obesity paradox seems to be explained in part by a combination of non-volitional weight loss related to occult disease and a protective effect of weight gain.

exercise test results and confirmed using the Veterans Affairs computerized medical records.

Statistical Analysis

NCSS software (Kayesville, Utah) was used for all statistical analyses. Unpaired *t* tests were used for comparisons of continuous variables, and chi-square tests were used to compare dichotomous variables between groups. Survival analysis was performed using Cox proportional hazards analysis to determine which clinical and exercise test variables were independently associated with all-cause and cardiovascular death. Survival analyses were adjusted for age, exercise capacity, and cardiovascular disease. Hazard ratios were calculated along with their 95% confidence intervals. The proportional hazards assumption was evaluated and confirmed using the scaled Schoenfeld residual. Kaplan–Meier survival curves were constructed between subjects exhibiting weight gain and weight loss, and compared using a log-rank test. A delta weight score was created so that units of weight change per year in pounds would be analogous to METs in a scale of 16, ranging from -8 to $+8$ lbs/year, allowing comparable change in percentage risk.

RESULTS

The sample included 3834 men with a mean age of 59 years (standard deviation [SD] ± 11), 75% of whom were white, 10% were black, 8% were Hispanic, and 7% were other. The mean follow-up period was 6.8 years (SD ± 3.1), and there were 314 deaths (8.2%) for an annual mortality of 1.1%; 23% of the deaths were due to cardiovascular disease. Weight parameters are presented in Table 1. The obesity paradox was present as reported previously in the VETS cohort with the survivors weighing 201 ± 38 lbs at baseline and those who died weighing 192 ± 40 lbs ($P < .001$). The population on average gained 0.8 lbs (SD ± 20) or 0.19

lbs/year (SD ± 6); 52% of the men gained weight or stayed the same, and 48% lost weight. Those who lost weight were on average 5 years older than those who gained weight ($P < .001$). The survivors gained 0.39 ± 6 lbs/year, and those who died lost 2.0 ± 9 lbs/year ($P < .001$).

Differences in body dimensions, historical data, risk factors, and exercise test responses between those who died and those who survived in the weight loss and weight gain groups are presented in Table 2. In the weight loss group, those who died had greater weight loss and weight loss per year than those who survived. Although the prevalence of pulmonary disease, renal failure, and cancer did not differ between the groups, both coronary artery disease and heart failure were more prevalent in those who died. Exercise capacity also was significantly lower in those who died (8.3 ± 3.0 vs 6.1 ± 3.0 METs, $P < .01$). Among those who gained weight, no differences were observed between those who died and those who survived in terms of weight parameters, but cardiovascular disease was significantly more prevalent among those who died. Similar to the weight loss group, exercise capacity was 33% higher among those who survived.

The annual mortality for those who gained weight was 0.8% compared with 1.7% for those who lost weight ($P < .001$, Figure 1). Stepwise age-adjusted proportional hazards analyses were performed initially for weight at the time of treadmill testing and then sequentially adding delta weight per year and exercise capacity (Table 3). Both exercise capacity and delta weight per year were significantly and independently associated with time to death, with the risk decreasing 18% for each MET achieved and increasing 4% per pound lost per year.

Table 4 shows causes of death for the entire cohort, for those who lost weight, and for those who gained weight. Subjects who lost weight had a higher proportion of deaths

Table 1 Weight Parameter Comparisons Based on Vital Status and Weight Gain or Loss

| Weight Parameters (mean \pm SD) | Entire Population (n = 3834) | | Deaths (All Cause) (n = 314) | | Deaths (Cardiac) (n = 72) | | Weight Gain (n = 1995) | | Weight Loss (n = 1839) | |
|-----------------------------------|------------------------------|----------------|------------------------------|-----------------|---------------------------|-----------------|------------------------|----------------|------------------------|--|
| | Survivors (n = 3520) | | | <i>P</i> Value* | | <i>P</i> Value* | | | <i>P</i> Value† | |
| Age, y | 59 \pm 11 | 59 \pm 11 | 67 \pm 11 | .000 | 68 \pm 10 | .000 | 57 \pm 10 | 62 \pm 11 | .000 | |
| Weight, lbs | 200 \pm 39 | 201 \pm 38 | 192 \pm 40 | .000 | 188 \pm 37 | .008 | 202 \pm 39 | 198 \pm 38 | .004 | |
| Height, in | 69 \pm 3 | 69 \pm 3 | 69 \pm 3 | .06 | 68 \pm 4 | .004 | 69 \pm 3 | 69 \pm 3 | .16 | |
| BMI, kg/m ² | 29 \pm 5 | 29 \pm 5 | 28 \pm 5 | .000 | 28 \pm 5 | .22 | 29 \pm 5 | 29 \pm 5 | .02 | |
| Obesity (%) | 1455 (38) | 1350 (38) | 105 (33) | .09 | 27 (38) | .99 | 783 (39) | 672 (37) | .09 | |
| Delta y | 6.8 \pm 3 | 6.9 \pm 3 | 5.9 \pm 3 | .000 | 5.9 \pm 3 | .03 | 6.8 \pm 3 | 6.8 \pm 3 | .79 | |
| Delta weight | 0.81 \pm 20 | 1.62 \pm 20 | -8.30 \pm 23 | .000 | -6.1 \pm 16 | .003 | 15 \pm 14 | -14.5 \pm 13 | .000 | |
| Delta weight/y | 0.19 \pm 6 | 0.39 \pm 5.7 | -2.0 \pm 8.6 | .000 | -0.97 \pm 11 | .09 | 3.1 \pm 5.2 | -3.0 \pm 5.1 | .000 | |
| Delta weight % | 0.52 \pm 9.8 | 0.94 \pm 9.5 | 4.1 \pm 11 | .000 | -3.1 \pm 8 | .001 | 7.5 \pm 6.9 | -7.1 \pm 6.0 | .000 | |
| Delta weight %/y | 0.12 \pm 3 | 0.22 \pm 2.8 | -1.0 \pm 4.4 | .000 | -0.49 \pm 6 | .08 | 1.6 \pm 2.7 | -1.5 \pm 2.4 | .000 | |

BMI = body mass index; SD = standard deviation. Obesity = BMI $>$ 30%; Delta years = time between clinic weights; Delta weight = change from weight between visits; Delta weight % = percent change from baseline weight.

**P* value for comparison with survivors.

†*P* value for comparison between weight gain and loss groups.

Table 2 Clinical, Historical, and Exercise Test Differences Between Those Who Survived and Those Who Died in the Group that Lost Weight (Mean \pm SD or Number [%])

| Variables | Weight Loss (N = 1839) | | | Weight Gain (N = 1995) | | |
|------------------------------------|------------------------|------------------------|---------|------------------------|------------------------|---------|
| | Died (n = 211) | Survived (n = 1628) | P Value | Died (n = 103) | Survived (n = 1892) | P Value |
| Age, y | 69 \pm 10 | 61 \pm 11 | <.01 | 62 \pm 10 | 57 \pm 10 | <.01 |
| Weight Parameters | | | | | | |
| Weight, lbs | 188 \pm 37 | 199 \pm 38 | <.01 | 199 \pm 45 | 202 \pm 38 | .54 |
| Height, in | 69 \pm 3 | 69 \pm 3 | .13 | 69 \pm 3 | 69 \pm 3 | .40 |
| BMI, kg/m ² | 28 \pm 5 | 29 \pm 5 | <.01 | 29 \pm 5 | 29 \pm 5 | .63 |
| Delta weight | -19.7 \pm 16.3 | -13.9 \pm 12.6 | <.01 | 15.0 \pm 16.2 | 15.0 \pm 13.8 | .98 |
| Delta weight/y | -4.9 \pm 8 | -2.8 \pm 4.5 | <.01 | 3.8 \pm 6.8 | 3.1 \pm 5.2 | .17 |
| Delta wt % | -9.9 \pm 7.5 | -6.7 \pm 5.8 | <.01 | 7.7 \pm 8.1 | 7.5 \pm 6.9 | .82 |
| Delta wt %/y | -2.5 \pm 3.9 | -1.4 \pm 2.2 | <.01 | 2.0 \pm 3.8 | 1.6 \pm 2.6 | .08 |
| Obesity (%) [$>$ 30% BMI] | 59 (28) | 618 (38) | .005 | 46 (45) | 737 (39) | .24 |
| Risk factors (%) | | | | | | |
| Diabetes | 47 (22) | 343 (21) | .68 | 26 (25) | 328 (17) | .04 |
| Hypertension | 130 (62) | 955 (59) | .41 | 59 (57) | 1022 (54) | .42 |
| Hypercholesterolemia | 56 (27) | 736 (45) | <.01 | 39 (38) | 809 (43) | .96 |
| Family CAD | 44 (21) | 392 (24) | .29 | 27 (26) | 513 (27) | .04 |
| Ever smoked | 146 (69) | 1070 (66) | .32 | 72 (70) | 1279 (68) | .23 |
| Current smoking | 49 (23) | 361 (22) | .73 | 29 (28) | 438 (23) | .24 |
| Alcohol abuse (history) | 4 (2) | 106 (7) | <.01 | 6 (6) | 138 (7) | .57 |
| Medical history (%) | | | | | | |
| Pulmonary disease | 23 (11) | 147 (9) | .37 | 14 (14) | 159 (8) | .06 |
| Chronic renal insufficiency | 2 (0.9) | 24 (1.5) | .54 | 1 (1) | 19 (1) | .97 |
| Cancer | 4 (1.9) | 28 (1.7) | .85 | 0 | 34 (2) | .17 |
| Cardiovascular diseases (%) | | | | | | |
| Typical angina | 20 (9) | 114 (7) | .19 | 15 (15) | 147 (8) | .01 |
| Myocardial infarction | 54 (26) | 220 (13) | <.01 | 29 (28) | 239 (13) | <.01 |
| CABG | 46 (22) | 96 (6) | <.01 | 17 (16) | 95 (5) | <.01 |
| PCI | 17 (8) | 84 (5) | .08 | 9 (9) | 89 (5) | .06 |
| Any CAD | 87 (41) | 402 (25) | <.01 | 47 (46) | 440 (23) | <.01 |
| Stroke | 8 (4) | 51 (3) | .61 | 6 (6) | 40 (2) | .01 |
| Claudication | 25 (12) | 53 (3) | <.01 | 4 (4) | 56 (3) | .59 |
| VHD | 7 (3) | 26 (1.6) | .07 | 0 | 23 (1) | .26 |
| Heart failure | 38 (18) | 70 (4) | <.01 | 16 (15) | 88 (5) | <.01 |
| Any HD | 93 (44) | 403 (25) | <.01 | 57 (55) | 529 (28) | <.01 |
| Exercise responses | | | | | | |
| Exercise capacity (METs) | 6.1 \pm 3 | 8.3 \pm 3.0 | <.01 | 6.7 \pm 2.3 | 8.9 \pm 3.1 | <.01 |
| Peak heart rate | 128 \pm 23 | 139 \pm 22 | <.01 | 129 \pm 23 | 142 \pm 22 | <.01 |
| Peak perceived exertion | 17 \pm 2 | 17 \pm 2 | .19 | 17 \pm 2 | 17 \pm 2 | .68 |
| ST depression \geq 1.0 mm | 44 (21) | 269 (17) | .11 | 27 (26) | 282 (15) | .002 |

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; HD = heart disease; MET = metabolic equivalent; PCI = percutaneous coronary intervention; VHD = valvular heart disease. *P* values represent comparisons within weight gain and weight loss groups. Any coronary artery disease = coronary artery bypass graft, myocardial infarction, percutaneous coronary intervention, or typical angina. Any heart disease = any of the conditions above.

attributable to heart failure and cancer, whereas deaths due to gastrointestinal causes were higher in the weight gain group. By including cancer, heart failure, renal failure, and 7 additional subjects who died of human immunodeficiency virus/autoimmune deficiency syndrome or hepatitis/cirrhosis, a total of 58.4% of the subjects in the weight loss group died of causes associated with cachexia (vs 26.8% in the weight gain group). The age, exercise capacity, and cardio-

vascular disease-adjusted hazard ratios for all-cause and cardiovascular mortality are presented as relative risks for subjects who exhibited no change in weight, weight gain, and weight loss in [Table 5](#), with no change in weight as the reference group. The weight gain groups had 36% and 24% reductions in all-cause and cardiovascular mortality, respectively, versus the no change group. In contrast, the weight loss groups demonstrated 49% and 25% higher all-cause and car-

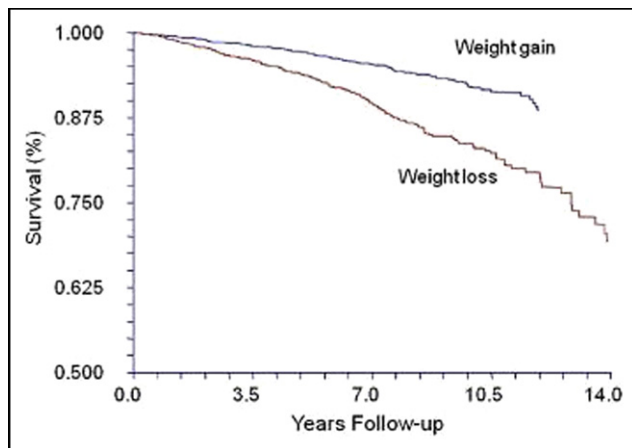


Figure 1 Kaplan-Meier survival curves for subjects exhibiting weight gain and weight loss. Log rank test $P < .01$ between groups.

diovascular mortality, respectively, versus the no change groups. These differences were significant for all-cause ($P < .001$) but not cardiovascular mortality ($P = .37$ and $.31$ for weight loss and weight gain groups, respectively). The results were similar when the analyses were repeated using a 2-lb weight change as the criterion for loss or gain.

DISCUSSION

We previously observed the existence of an “obesity paradox” in veterans referred for exercise testing for clinical reasons, in which overweight individuals exhibited better survival than normal weight subjects.^{6,7,17} Most previous studies addressing the obesity paradox have been limited to a measure of body dimensions at a single baseline visit, and the effects of *changes* in weight have not been fully explored. The current results suggest that this phenomenon is explained in part by weight loss associated with conditions linked to muscle wasting. Weight loss had a significant and independent relationship to all-cause mortality, as demonstrated by a 4% increase in mortality per pound lost over the mean follow-up of 7 years, in contrast with the comparatively lower mortality rate among those exhibiting weight gain (Figure 1).

One possible explanation for the weight loss and higher mortality we observed is occult disease. It is surprising that clinical assessment of baseline health status did not detect the illnesses that cause weight loss and mortality, but the current data suggest that these illnesses exist. The decline in weight was evident even after accounting for weight loss associated with terminal events. The concept that the obesity paradox in our sample is partly attributable to occult disease is underscored by the fact that two thirds of the deaths occurred in the weight loss group, and approximately 60% of these were due to conditions associated with muscle wasting. Notably, most of these conditions were not apparent at the time of the treadmill test but were diagnoses that were made during the mean 7-year follow-up. Previous

studies on the obesity paradox have generally reported *all-cause* mortality, but few have assessed *specific causes* of death. The majority of these studies have removed subjects with potentially wasting conditions at baseline, as was the case in our previous studies;⁶⁻⁸ therefore, little is known regarding the effect of these conditions on the obesity paradox. In addition to serial measures of weight status, a unique feature of the current study was the fact that causes of death were carefully determined from computerized medical records during the follow-up. The higher mortality associated with weight loss and chronic conditions, including cancer and heart failure (Table 4), suggests that occult disease contributed in part to the obesity paradox.

Although the obesity paradox has been described in a number of clinical populations over the last decade,^{2,4} there are few studies assessing weight change.^{2,13,14} Even in populations in whom excess weight has been associated with poor health outcomes, weight loss in some studies has been associated with increased mortality.²²⁻²⁴ In the Multiple Risk Factor Intervention Trial, weight variation (both gain and loss) over a 6- to 7-year period was associated with higher cardiovascular and all-cause mortality compared with those whose weight remained stable.²⁴ Those who lost weight had slightly worse outcomes than those who gained weight. In the Established Populations for Epidemiologic Studies of the Elderly Study, those who lost 10% or more of body weight between age 50 years and old age had the highest risk of mortality (relative risk = 1.6). Exclusion of participants who lost 10% or more of their weight and adjustment for health status eliminated the higher risk of death associated with low weight. The authors suggested that the inverse association between weight and mortality in old age reflects illness-related weight loss from heavier

Table 3 Age-Adjusted Proportional Hazards Analysis with All-Cause Mortality as the Outcome for Each Predictor Alone and Combined

| | Hazard Ratio | 95% Confidence Interval | P Value | Regression Coefficient |
|------------------------------|--------------|-------------------------|---------|------------------------|
| Univariate Analysis | | | | |
| Baseline weight | 1.00 | 0.99-1.00 | .98 | -0.00 |
| Exercise capacity | 0.82 | 0.78-0.86 | <.0001 | -0.20 |
| Delta lbs/y | 0.96 | 0.94-0.97 | <.0001 | -0.04 |
| Multivariate Analysis | | | | |
| Model 1 | | | | |
| Baseline weight | 0.99 | 0.99-1.00 | .86 | -0.00 |
| Delta lbs/y | 0.96 | 0.95-0.97 | <.0001 | -0.04 |
| Model 2 | | | | |
| Exercise capacity | 0.82 | 0.78-0.86 | <.0001 | -0.19 |
| Delta lbs/y | 0.96 | 0.95-0.97 | <.0001 | -0.03 |
| Model 3 | | | | |
| Baseline weight | 0.99 | 0.99-1.00 | .13 | -0.002 |
| Exercise capacity | 0.82 | 0.78-0.86 | <.0001 | -0.20 |
| Delta lbs/y | 0.96 | 0.95-0.97 | <.0001 | -0.04 |

Table 4 Causes of Death in the Entire Cohort and the Weight Loss and Weight Gain Groups

| | All Deaths (n = 314) | Deaths in Weight Loss Group (n = 206) | Deaths in Weight Gain/No Change Group (n = 108) | P Value* |
|---------------------|-------------------------|--|--|----------|
| Causes of Death (%) | | | | |
| Heart failure | 25 (7.9) | 21 (10.2) | 4 (3.7) | .01 |
| Cancer | 93 (29.6) | 78 (37.9) | 15 (13.9) | .000 |
| Gastrointestinal | 44 (14.0) | 17 (8.3) | 27 (25.0) | .000 |
| Pulmonary | 42 (13.4) | 25 (12.1) | 17 (15.7) | .37 |
| All cardiac | 72 (22.9) | 47 (22.8) | 25 (23.1) | .95 |
| Renal | 24 (7.6) | 14 (6.8) | 10 (9.3) | .43 |
| Neurologic | 25 (7.8) | 16 (7.8) | 9 (8.3) | .86 |
| Accidents/suicide | 1 (0.3) | 0 | 1 (0.9) | .16 |
| Others | 13 (4.1) | 9 (4.4) | 4 (3.7) | .78 |

*Comparison between weight loss and weight gain groups.

weight in middle age.²⁵ Strandberg and associates²² evaluated 1114 men in 1974 and again in 2000, and reported that among groups who gained, lost, or maintained body weight, the group who lost weight had the highest rate of late-life comorbidities and the greatest total mortality, with a relative risk of 2.0 compared to the group with stable weight across the follow-up. Most recently, Lavie et al²³ followed 529 cardiac rehabilitation participants for 3 years and observed only a slight trend for lower mortality among patients who lost weight.

The concept that the relationship between lower weight and higher mortality in the current study and others^{2,4-8,11,15,17,22-26} results from *unintentional* weight loss is important to consider. Numerous studies in cardiac rehabilitation and other settings in which clinically supervised (intentional) weight loss occurred have shown extensive health benefits, including a lower incidence of cardiovascular events and better overall survival.^{1-3,27,28} Intentional weight loss has been associated with marked reductions in the metabolic syndrome, inflammatory markers, lipids, prevalence of hypertension, and better glucose tolerance.²⁹ Several of the original observations on the obesity paradox were made in the context of patients with heart failure,^{17,30} and studies have shown that weight loss can

reduce left ventricular mass and ameliorate both systolic and diastolic dysfunction.^{31,32} Although long-term studies are lacking, gastric bypass surgery has been consistently associated with considerable reductions in markers of cardiovascular risk,^{33,34} and limited available data suggest that surgical weight loss results in reduced morbidity and mortality.³⁵ Despite the obesity paradox, these studies support clinically supervised weight reduction, particularly in patients with or at high risk for cardiovascular disease.

Limitations

A complete explanation of the contribution of weight change to the obesity paradox would require a detailed examination of latent disease, which would be a difficult undertaking. Our findings are limited to men. The VETS study consists of men referred for exercise testing for clinical reasons, and although cardiovascular and other diseases were ruled out in the majority, the test was conducted for clinical reasons. We do not have data on waist circumference or fat distribution, factors that have been suggested to contribute the obesity paradox;^{36,37} we only measured body mass index, which may not adequately capture the health effects of obesity.³⁸ Finally, we have previously reported that the obesity paradox is negated in subjects with high

Table 5 Relative Risks for All-Cause and Cardiovascular Mortality Among Weight Gain and Weight Loss Groups Relative to the No Change (Reference) Group, with Multivariate Adjustments

| Adjustment | Reference | Weight Gain | Weight Loss |
|--|-----------|------------------|------------------|
| All-Cause Mortality | | | |
| Age | 1.0 | 0.61 (0.47-0.78) | 1.60 (1.26-2.03) |
| Age and exercise capacity | 1.0 | 0.63 (0.49-0.81) | 1.51 (1.19-1.92) |
| Age, exercise capacity, and cardiovascular disease | 1.0 | 0.64 (0.50-0.83) | 1.49 (1.17-1.89) |
| Cardiovascular Mortality | | | |
| Age | 1.0 | 0.66 (0.39-1.11) | 1.46 (0.89-2.41) |
| Age and exercise capacity | 1.0 | 0.71 (0.42-1.18) | 1.35 (0.82-2.23) |
| Age, exercise capacity, and cardiovascular disease | 1.0 | 0.76 (0.45-1.28) | 1.25 (0.76-2.07) |

Cardiovascular disease includes history of myocardial infarction, coronary artery disease, heart failure, stroke, or bypass surgery; 95% confidence intervals are in parentheses.

fitness,^{6,7} and we do not have serial measures of fitness in our subjects. Therefore, the extent to which fitness level interacted with weight change and mortality is unknown.

CONCLUSIONS

Weight loss over a mean 7-year period was related to higher all-cause mortality in veterans who were referred for exercise testing for clinical reasons. The obesity paradox in our sample seems to be explained in part by non-volitional weight loss related to latent disease that contributes to early mortality. The obesity paradox is a complex phenomenon that requires additional study, and future studies should consider weight change when evaluating the longitudinal association among health, overweight/obesity, and outcomes.

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