Animal experiments have shown that calorically restricted (CR) animals weigh less and live longer than their ad libitum-fed peers. Are these observations applicable to human beings? This is an important question because the prevalence of obesity in America has increased markedly over recent years. We examine whether there are physiologic effects that occur with CR in humans that could plausibly explain the observed longevity of laboratory animals associated with CR. We also review epidemiologic data from observational and interventional studies on the relationships of caloric intake, energy balance, and weight gain with age-related diseases and longevity. Additionally, data on whether long-term, sustained maintenance of weight loss is feasible, as well as the degree of CR achieved in clinical trials, are summarized. Finally, we provide recommendations regarding further epidemiologic research that will help clarify unanswered questions in these areas.

Panel 1 members had extensive discussions regarding the definition of caloric restriction (CR) in animal experiments and its applicability to human beings. In animal studies, experimental manipulation results in CR animals that weigh less than those fed ad libitum (AL). There also is a dose-response gradient—within an experiment, the most calorically restricted animals are the smallest animals. It is unlikely that the approach to CR used in various experimental rodent models (allowing the intervention group access to fewer calories per day than the AL-fed control group) can be directly applied to studies of free-living humans, and it would be impossible to apply it experimentally over a human life span. Therefore, we must consider different models of caloric restriction that are more applicable to humans.

What is an appropriate caloric restriction model in humans? Is it:

- Being thin over most of adult life?
- Not gaining weight over time?
- Eating fewer calories so weight is lost?
- Expending more calories than eaten?
- Eating fewer calories than one wants?
- Eating fewer calories than average (e.g., for one’s age, sex, height)?

Because it is unclear what the appropriate caloric restriction model might be in humans, we propose that studies of CR in humans make use of one characteristic (which we will call a phenotype) observed in animal experiments of CR: not gaining weight after early adulthood, excluding pregnancy. However, we are aware of some limitations of using this phenotype. Different individuals achieve lifetime weight stability through various means, and weight stability may not necessarily be due to low levels of caloric intake. Some individuals may indeed consume fewer calories than the average person to achieve this weight stability, whereas others may actually consume more calories than average but balance this intake with a higher-than-average energy expenditure.

Panel 1 also believes that it is not useful to conduct further studies regarding issues that have been clearly established. Based on existing epidemiologic data, we know that:

- Human populations in industrialized societies become progressively heavier as they grow older.
- If weight gain is prevented, some metabolic risk factors are more likely to remain normal.
- Experimental studies of weight reduction over the relatively short term (i.e., on the order of 1–3 years) have shown improvements in blood pressure, lipids, and glu-
cose tolerance. These experiments have been conducted primarily among overweight subjects.

- Individuals who avoid overweight and obesity have decreased risks of type 2 diabetes and hypertension.
- Maintaining a stable weight reduces the risk of coronary heart disease (CHD), cardiovascular disease (CVD), and all-cause mortality.

The key issues addressed by this panel were:

- Are there physiologic effects that occur with CR in humans that could plausibly explain the observed longevity of laboratory animals associated with CR?
- Are there data (both observational and interventional) to indicate that caloric restriction can prevent age-related diseases?
- Are there data to indicate that long-term, sustained maintenance of weight loss is feasible?
- What degree of CR has been achieved in clinical trials?

**Background Information**

**Prevalence of Overweight and Patterns of Weight Change**

The prevalence of overweight (body mass index \([\text{BMI}]\) 25.0–29.9) has changed little among men and women aged 20–74 years in the United States between the first National Health Examination Survey (NHES I), 1960–1962, and the third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 (30.5% and 32.0%, respectively) (1). However, the prevalence of obesity (BMI greater than or equal to 30) has shown a marked increase over recent years (NHES I, 1960–1962, 12.8%; NHANES I, 1971–1974, 14.1%; NHANES II, 1976–1980, 14.5%; NHANES III, 1988–1994; 22.5%). Trends are generally similar for all age, gender, and race groups. Across the age range of 20–74 years in NHANES III, the prevalence of obesity increased with age among both men and women, reaching a maximum at ages 50–59 years and decreasing somewhat after that.

It is dismaying to note that more than half the adult population of the United States today exceeds the healthy weight range. Within certain subgroups, the prevalence of overweight and obesity (BMI greater than or equal to 25) is even higher; for example, 72.9% among non-Hispanic white men aged 50–59, and 78.1% among non-Hispanic black women aged 50–59 (1).

People living in industrialized societies appear to gain weight after early adulthood. Much of the data supporting this observation derive from cross-sectional surveys, such as those described above. Few published reports document the pattern of weight change during the adult years longitudinally within a defined cohort. Examples of patterns of weight change with age observed longitudinally among three populations (the Aerobics Center Longitudinal Study, the Harvard Alumni Health Study, and the Honolulu Heart Study) are provided in Appendix A.

Epidemiologic data clearly show that overweight is associated with numerous risk factors for chronic diseases: increased incidence of CVD; hypertension; type 2 diabetes; gallbladder disease; cancers of the endometrium, breast, prostate, and colon; osteoarthritis; disability; sleep apnea; and increased mortality from CVD and all causes [reviewed in (2)]. The critical question is whether CR or weight loss, with or without ancillary measures such as physical activity, result in decreased incidence of such chronic diseases and increased longevity. In laboratory animals, experiments dating from the early part of this century suggest that CR is associated with greater longevity. The following sections summarize data from epidemiologic studies regarding the extent to which these observations in animals are applicable to humans. One limitation of these epidemiologic studies is that weight, or weight adjusted for height (e.g., BMI), has been the variable usually studied, as this is easily measured in the large numbers of subjects that are needed for the study of chronic diseases. Although overweight is generally correlated with excess body fat, this is by no means an exact measure of body fat. Experimental studies examining short-term outcomes, such as changes in body weight and body composition, have enrolled fewer subjects and have been able to assess body fat and lean body mass more directly. These studies are reviewed by another panel.

**Observational Studies of CR or Weight Loss and Morbidity/Mortality**

**Body weight and morbidity/mortality.**—There is a lack of consensus regarding whether the lowest risk of chronic diseases occurs among the thinnest individuals. Study results are inconsistent as to where the nadir of risk occurs, and there is no consensus on whether the relation between BMI and health outcomes is linear or J-shaped. Yet, when subgroups of healthy, nonsmoking people are followed, those who are lean appear to be at relatively low risk (3–5).

**Caloric restriction and morbidity/mortality.**—Several natural history studies of populations undergoing caloric deprivation during war and ecologic studies comparing calorie-deprived populations with those that are not suggest that there are lower body weights and fewer obesity-related diseases in calorie-deprived populations than in those with adequate food supplies. Such observations, however, suffer from potential bias and lack of generalizability to stable societies.

Unique human data are available for four men and women who were confined inside Biosphere 2 for 2 years (6–8). During this period, food availability was severely restricted (although food quality remained high), resulting in restriction of energy intake to an average of 1780 kcal/day without malnutrition. Significant weight loss occurred: 74 to 62 kg (163 to 137 lb) in men and 61 to 54 kg (135 to 119 lb) in women. This was associated with decreases in systolic and diastolic blood pressure, as well as levels of total cholesterol, triglycerides, and fasting glucose. It remains to be seen whether such changes will ultimately result in greater longevity. One obvious limitation of these data is the small sample size.

We examined variables that might be related to caloric restriction in the Aerobics Center Longitudinal Study and the Harvard Alumni Health Study. In 1988, men participating in the Harvard Alumni Health Study were asked, “How often are you dieting (eating less than you would like)?” Re-
response options were never, rarely, sometimes, often, or always. This question is likely to elicit reasonably valid responses, as evidenced by data from the Aerobics Center Longitudinal Study showing that among both men and women, those who often dieted weighed the most while those who rarely dieted weighed the least (Figures 1 and 2). Self-reports of dieting may be valid indicators of eating behavior, but the limited data presented here suggest that dieting behavior is not the same as the phenotypic manifestation of caloric restriction as used in this report, namely, not gaining weight after early adulthood.

Among 9,211 Harvard men with a mean age of 67 years who were free of cardiovascular disease and cancer in 1988, 645 died between 1988 and 1993. In age-adjusted analyses, it appeared that those who reported sometimes dieting in 1988 were 20% less likely to die during follow-up than those who never dieted (Table 1). However, after adjusting for potential confounders, there no longer was any association between the frequency of dieting and all-cause mortality.

Weight loss and morbidity/mortality.—In prospective studies, adults who gain or lose weight (or, more generally, have increased weight variability) tend to have increased incidence of CVD, diabetes, and disability, as well as increased mortality from all causes, CVD, and non-CVD causes, when compared with adults who remain weight-stable (9–24). There are some exceptions to this across studies, or among subgroups within studies. In some of these studies, the period of weight variability was assessed over decades, and in others it was measured over shorter periods. As indicated earlier, it is not possible by these studies to determine if individuals who remained weight stable achieved this by relatively low caloric intake, or by balancing a high intake with an equally high expenditure of energy.

Observational data from the aforementioned studies of weight variability may be biased (25). People who develop chronic diseases often lose weight, creating a spurious association between weight loss and disease status. Excluding individuals with known disease at baseline or those with disease early in follow-up may not completely eliminate this bias (26). Few studies have attempted to distinguish voluntary from involuntary weight loss (27–31), and the validity of doing so is suspect because volition is hard to define. For example, if a person takes up walking for recreation and loses weight, is that weight loss voluntary or involuntary? Also, a person may intend to lose weight, subsequently achieve weight loss, and interpret this loss as volitional; yet the weight loss may actually have been the result of occult illness. Further, a person may choose to voluntarily lose weight but it may take time for his or her risk to fall to low levels even with successful weight loss. The few existing studies suggest that what appears to be a hazard associated with weight loss in observational studies is due to involuntary weight loss, and that losing weight voluntarily probably does not cause harm. For example, the Iowa Women’s Health Study recently showed that intentional weight loss episodes of 9.1 kg (20 lb) or more were not associated with significantly higher or lower total or CVD mortality compared with never losing 9.1 kg or more. Women with unintentional weight loss of 9.1 kg or more had significantly higher total mortality risk of 26–57%, and a 51–114% higher CVD mortality risk, compared with women who never lost 9.1 kg or more over the period of follow-up (30).

### Table 1. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Death Between 1988 and 1993 among 9,211 Harvard Alumni

<table>
<thead>
<tr>
<th>Frequency of Dieting</th>
<th>Neatly</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often/Always</th>
<th>p, Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>212</td>
<td>182</td>
<td>141</td>
<td>110</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>0.87</td>
<td>0.80</td>
<td>1.01</td>
<td>0.52</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(referent) (0.71–1.06) (0.64–0.99)</td>
<td>(0.80–1.27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate HR</td>
<td>1.00</td>
<td>0.90</td>
<td>0.92</td>
<td>0.93</td>
<td>0.66</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(referent) (0.69–1.16) (0.70–1.23)</td>
<td>(0.68–1.27)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Without cardiovascular disease and cancer according to frequency of dieting assessed in 1988. Frequency of dieting was assessed with the question: “How often are you dieting (eating less than you would like)? 1. Never; 2. Rarely; 3. Sometimes; 4. Often; 5. Always.”

1Adjusted for age, body mass index, smoking status, physical activity, parental death <65 years, alcohol intake, red meat intake, vegetable intake, vitamin/mineral supplements, and history of hypertension and diabetes mellitus; all assessed in 1988.
In the Swedish Obese Subjects study, patients who elected to undergo gastric reduction surgery experienced greater weight loss (−17%) than patients who chose conventional weight reduction therapy (+1%) after 6 years. The surgery group had a far lower prevalence of diabetes compared with the diet group (8.5% vs 20%, \( p < .0001 \)) (32). Preliminary analyses also suggest lower mortality in the surgery group (33,34). In this study, greater amounts of weight loss were also associated with better quality of life (35).

**Intervention Studies of Weight Loss and Risk Factors/Morbidity**

Most clinical trials examining the effect of weight loss (achieved through diet and/or exercise) have had as their primary outcome the modification of cardiovascular risk factors. The most common endpoints are alterations of blood pressure, lipid profile, and glucose tolerance, with only a few trials targeting clinical endpoints such as angina pectoris or myocardial infarction. Most studies have been conducted among apparently healthy participants, although a few have been conducted among individuals with previous cardiovascular disease. In these studies, most participants achieved only slight to moderate alterations in weight. Representative trials are presented in Tables 2–4.

**Trials of weight loss and blood pressure.**—The effect of weight reduction on blood pressure has been examined in several trials. The Hypertension Control Program (36), using a multifactorial approach (CR, sodium and alcohol reduction), showed that a mean weight loss of 1.8 kg (4 lb) yielded a higher rate of discontinuation of antihypertensive medication (39%) than observed among the control group (5%). The Trials of Hypertension Prevention Phase I (37) assessed the effect of weight loss (CR and increased physical activity) on blood pressure among 564 obese men and women aged 30 to 54 years with diastolic blood pressure (DBP) between 80 and 89 mm Hg. After 18 months, mean weight loss was 4.7±0.5 kg among men and 1.8±0.8 kg among women in the intervention group. The mean change in DBP for the intervention participants compared with controls was −2.8±0.6 mm Hg for men and −1.1±0.9 mm Hg for women. A similar result was obtained for systolic blood pressure (SBP).

Three trials compared separately the effects of weight loss and reduced sodium intake. In the Hypertension Prevention Trial (38), the most impressive reduction was seen among participants in the CR group, with decreases in DBP of 2.8 mm Hg and in SBP of 2.4 mm Hg accompanying a 4% reduction in body weight. In the Trials of Hypertension Prevention Phase II (39), intervention groups were successful in reducing blood pressure in the short term, though the intervention effect generally decreased with continued follow-up, except in the weight loss group. At termination of the trial, blood pressure reductions remained higher in the weight-loss groups than in the usual-care group (−1.1±0.5 mm Hg for SBP, −1.0±0.4 mm Hg for DBP). The Trial of Nonpharmacologic Interventions in the Elderly (40) extended these findings to an elderly population. These studies clearly demonstrate the efficacy of weight loss and sodium restriction, alone or combined, in reducing blood pressure or in preventing development of hypertension.

**Trials of weight loss and lipid profile.**—Previous trials have shown that weight reduction can improve lipid profiles. However, the comparative role of energy-restricted diets and physical activity—and their interaction—is still not clear, nor have the relative efficacies of reduced-fat diets and hypocaloric diets been established.

In the Stanford Weight Control Project I (41), a one-year trial of 131 overweight men aged 30 to 59 years, both exclusive dieters and exclusive exercisers lost significant amounts of weight: a mean of −7.8 kg (−17.2 lb) of total body weight and −5.6 kg (−12.3 lb) of fat weight for the exclusive dieters, and −4.6 kg (−10.1 lb) of total body weight and −3.8 kg (8.3 lb) of fat weight for the exclusive exercisers. When compared with the control group, both intervention groups had significant increases in plasma concentrations of high-density lipoprotein cholesterol (HDL-C) and significant decreases in triglyceride levels, but levels of total and low-density lipoprotein cholesterol (LDL-C) were not significantly changed. Thus, fat loss generated by either dieting or exercising produced comparable and favorable changes in HDL-C and triglycerides. The Stanford Weight Control Project II (42) tested the hypothesis that exercise increases HDL-C levels in people who adopt a diet such as that defined by the National Cholesterol Education Program (NCEP). This one-year trial assigned 264 moderately overweight, sedentary men and women aged 25 to 49 years to one of three groups: control, hypocaloric NCEP diet, or hypocaloric NCEP diet with exercise. Mean fat loss in the intervention groups ranged from 4.0 kg to 7.8 kg (8.8 to 17.2 lb). Weight loss on the NCEP diet alone did not significantly change HDL-C levels in either men or women as compared with controls. Plasma HDL-C levels increased significantly more in the men who exercised and dieted (+13±3%) than in the men who only dieted (+2±3%) or the control men (−4±2%). HDL-C levels were higher in the women who exercised and dieted (+1±2%) compared with women who only dieted (−10±3%) and declined slightly in the control group (−3±3%). The same research group addressed the impact of diet and exercise on people with dyslipidemia (43). In a one-year trial, 180 postmenopausal women and 197 middle-aged men, all with moderate lipid alterations, were randomly assigned to aerobic exercise, an NCEP Step 2 diet, diet plus exercise, or to a control group that received no intervention. In women and men in both the diet and the diet-plus-exercise groups, intake of fat and cholesterol decreased significantly during the study, as did body weight. In the exercise-only group and in the controls, neither dietary intake nor body weight decreased. Changes in HDL-C and triglyceride levels did not differ significantly among the treatment groups for subjects of either sex. In the diet-plus-exercise group, serum LDL-C levels were significantly reduced among women (−14.5±22.2 mg/dl) and men (−20.0±17.3 mg/dl) compared with the control group. The reduction in LDL-C in men in the diet-plus-exercise group was also significant compared with the reduction among men in the exercise-only group (−3.6±18.8 mg/dl). In contrast, the observed reductions in LDL-C levels in the diet-
Table 2. Randomized Trials of Blood Pressure Reduction With Weight Reduction Interventions (Diet and/or Exercise)

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Study Population</th>
<th>Length</th>
<th>Interventions</th>
<th>Endpoint</th>
<th>Weight Loss</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension Control Program, 1987 [36]</td>
<td>158 overweight men and women aged 35+ with drug-controlled hypertension</td>
<td>4 years</td>
<td>1. Reduce BW, alcohol, and sodium intake, and discontinue antihypertensive medication 2. No dietary change, only drug discontinuation 3. No dietary change, drugs maintained</td>
<td>Being normotensive without drug therapy</td>
<td>Mean WL of 1.8 kg; 30% of group 1 maintained 4.5 kg WL</td>
<td>39% in group 1 remained normotensive compared with 5% in group 2.</td>
</tr>
<tr>
<td>Trials of Hypertension Prevention (TOHP) I, 1993 [37]</td>
<td>564 men and women aged 30–54 within 155–165% of DBW and with DBP of 80–89 mm Hg</td>
<td>18 months</td>
<td>1. Usual care 2. Weight reduction of at least 4.5 kg in the first 6 months using diet + exercise</td>
<td>Office BP</td>
<td>At 6, 12, and 18 months of follow-up: 6.5, 5.6, and 4.7 kg for men and 3.7, 2.7, and 1.6 kg for women</td>
<td>DBP for intervention compared with controls: –2.8 mm Hg for men and –1.1 mm Hg for women. For SBP, –3.1 mm Hg for men and –2.0 mm Hg for women. BP reductions were greater for those who lost larger amounts of weight.</td>
</tr>
<tr>
<td>Hypertension Prevention Trial, 1990 [38]</td>
<td>841 healthy men and women aged 25–49 with DBP of 78 to 89 mm Hg</td>
<td>3 years</td>
<td>1. Usual care 2. Weight control (to DBW) 3. Reduced sodium 4. Weight control + reduced sodium 5. Reduced sodium + increased potassium</td>
<td>Office BP</td>
<td>Group 2: –1.63 kg; Group 3: +0.68 kg; Group 4: –0.14 kg</td>
<td>Lower mean blood pressure in all four intervention groups, with the largest net reduction in group 2 of 5.1 mm Hg in DBP and 2.4 mm Hg in SBP at 3 years. Fewer hypertensive events in all four intervention groups; significantly fewer in group 3.</td>
</tr>
<tr>
<td>Trials of Hypertension Prevention (TOHP)-II, 1997 [39]</td>
<td>2,382 men and women aged 30–54 within 110–165% of DBW and DBP of 83–89 mm Hg not on anti-hypertensive drugs</td>
<td>36 months</td>
<td>1. Usual care 2. Weight loss to DBW or at least 4.5 kg 3. Reduced sodium 4. Weight loss + reduced sodium</td>
<td>Office BP</td>
<td>2 kg at 36 months in the weight loss and combined groups compared with weight changes in the usual care group</td>
<td>Compared with the usual care group, BP decreased 1.30/0.9 mm Hg in the WL group, 1.2/0.7 mm Hg in the sodium reduction group, and 1.1/0.6 mm Hg in the combined group at 36 months. Differences were statistically significant for SBP/DBP in the WL-group and for systolic BP in the sodium reduction group. Through 48 months, the incidence of hypertension was significantly less in each intervention group than the usual care group.</td>
</tr>
<tr>
<td>Trial of Nonpharmacologic Interventions in the Elderly (TONE), 1998 [40]</td>
<td>975 men and women aged 60–80 on antihypertensive therapy (585 obese)</td>
<td>15–36 months (mean, 29 months)</td>
<td>Obese participants: 1. Usual care 2. WL of 4.5 kg or greater 3. Reduced sodium 4. WL + reduced sodium Nonobese participants: 1. Usual care 2. Reduced sodium</td>
<td>Diagnosis of high blood pressure, treatment with antihypertensive medication, or CVD event</td>
<td>Obese participants: usual care, –0.9 kg; weight loss groups, –3.9 kg</td>
<td>Among obese participants, odds ratios for being free of endpoint compared with controls were 0.64 (95% CI 0.49–0.85) for WL, 0.60 (95% CI 0.45–0.80) for sodium restriction, and 0.47 (95% CI 0.35–0.64) for WL + sodium restriction.</td>
</tr>
</tbody>
</table>

### Table 3. Randomized Trials of Lipoprotein Levels, Blood Glucose, and Insulin With Weight Reduction Interventions (Diet and/or Exercise)

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Study Population</th>
<th>Length</th>
<th>Interventions</th>
<th>Weight Loss</th>
<th>Lipids</th>
<th>Blood Glucose and Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stanford Weight Control Project I (SWCP-I), 1988 [41]</strong></td>
<td>155 sedentary men aged 35–59 within 120–150% of DBW</td>
<td>1 year</td>
<td>1. Usual care 2. Weight loss by diet (no change in activity) 3. Weight loss by increased aerobic activity (no change in diet)</td>
<td>−7.8 kg in dieters, −6.2 kg in exercisers</td>
<td>WL by diet or exercise increased HDL-C, decreased TG, had no significant impact on LDL-C. No difference between diet and exercise group.</td>
<td></td>
</tr>
<tr>
<td><strong>Stanford Weight Control Project II (SWCP-II), 1991 [42]</strong></td>
<td>132 men (BMI 28–34) and 132 premenopausal women (BMI 24–30) aged 25–49</td>
<td>1 year</td>
<td>1. Control 2. NCEP step I diet 3. NCEP step I diet + aerobic exercise</td>
<td>Men: diet only, −6.8 kg; diet+exercise, −10.4 kg. Women: diet only, −5.4 kg; diet+exercise, −6.4 kg</td>
<td>Men: diet+exercise increased HDL-C and decreased TG vs other groups. Women: diet only decreased HDL-C; diet+exercise increased HDL-C and decreased TG. In both men and women, diet+exercise improved HDL-C compared with diet only and improved lipid profile compared to controls.</td>
<td></td>
</tr>
<tr>
<td><strong>Stefanick et al., 1998 [43]</strong></td>
<td>180 postmenopausal women aged 45–64 and 197 men aged 30–64 with low HDL and high LDL</td>
<td>1 year</td>
<td>1. Control 2. NCEP step II diet 3. Exercise, no dietary change 4. NCEP step II diet + exercise</td>
<td>Control, +0.8 kg; diet alone, −2.7 kg; exercise alone, −0.4 kg; diet+exercise, −3.1 kg</td>
<td>No change in HDL-C, TG, or HDL/TG ratio among treatment groups. LDL-C significantly reduced in diet+exercise group (both women and men) compared with control, and compared with exercise only for men. LDL-C not significantly reduced in diet only group (both men and women) compared with controls.</td>
<td></td>
</tr>
<tr>
<td><strong>Katzel et al., 1995 [44]</strong></td>
<td>170 men aged 46–80 within 120–160% of DBW</td>
<td>9 months</td>
<td>1. Control 2. WL (diet similar to NCEP step I) 3. Aerobic exercise</td>
<td>−9.5 kg in WL group</td>
<td>Compared with controls, HDL-C significantly increased (13%) in WL, but not exercise group, while TG, TC, and LDL-C decreased in both groups.</td>
<td>WL, but not exercise, decreased fasting insulin and glucose concentrations, 2-hour glucose areas during OGTT, and HDL-C. Both decreased 2-hour insulin areas during OGTT.</td>
</tr>
</tbody>
</table>

**Note:** BMI: body mass index; DBW: desirable body weight; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol, NCEP: National Cholesterol Education Program; OGTT: oral glucose tolerance test; TC: total cholesterol; TG: triglycerides; WL: weight loss.
Table 4. Randomized Trials of Weight Reduction Interventions (Diet and/or Exercise) in Individuals With Previous Coronary Disease

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Study Population</th>
<th>Length</th>
<th>Intervention</th>
<th>Endpoint</th>
<th>Weight Loss</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford Coronary Risk Intervention Project (SCRIP), 1994 [46]</td>
<td>300 men and women aged 25–65 with angiographically documented CAD (82% with comparative measurements of segments with visible disease at baseline and follow-up)</td>
<td>4 years</td>
<td>1. Usual care 2. Multifactorial risk reduction (diet low in fat and cholesterol, weight loss, increased physical activity, smoking cessation, and medication to favorably alter lipoprotein profiles)</td>
<td>Rate of change in minimal diameter of diseased coronary segments</td>
<td>Intervention group: mean 4% decrease in weight and 20% increase in exercise capacity; small changes in usual care group</td>
<td>Intervention group: rate of narrowing of diseased coronary artery segments was 47% lower than in usual-care group (change in minimal diameter, (-0.024 \pm 0.066 \text{ mm/y}) versus (-0.045 \pm 0.073 \text{ mm/y}; p &lt; .02). 25 hospitalizations in the intervention group vs 44 in the usual-care group (RR, 0.61; 95% CI, 0.4 to 0.9; (p = .05)).</td>
</tr>
<tr>
<td>Lifestyle Heart Trial (1-year follow-up) [47]</td>
<td>41 men and women aged 35–75 with angiographically documented CAD</td>
<td>1 year</td>
<td>1. Usual care 2. Multifactorial risk reduction (low-fat vegetarian diet, exercise, smoking cessation, stress management)</td>
<td>Change in coronary stenosis</td>
<td>(-10.8 \text{ kg in intervention group, } +1.4 \text{ kg in usual care group})</td>
<td>Average diameter stenosis regressed from 40.0% to 37.8% in the risk-reduction group and progressed from 42.7% to 46.1% in the control group. For lesions &gt;50% stenosed, the average percentage diameter stenosis regressed from 61.1% to 55.8% in the risk-reduction group and progressed from 61.7% to 64.4% in the control group.</td>
</tr>
<tr>
<td>Lifestyle Heart Trial (5-year follow-up) [48]</td>
<td>35 men and women aged 35–75 with angiographically documented CAD</td>
<td>5 years</td>
<td>1. Usual care 2. Multifactorial risk reduction (low-fat vegetarian diet, exercise, smoking cessation, stress management)</td>
<td>Change in coronary stenosis and cardiac events</td>
<td>(-5.8 \text{ kg from baseline} (+5 \text{ kg from one-year follow-up}))</td>
<td>Average percent diameter stenosis regressed by 3.1 absolute percentage points from baseline in the risk-reduction group (7.9% relative improvement) and progressed by 11.8 percentage in controls (27.7% worsening). 25 cardiac events occurred in 28 risk-reduction patients vs 45 events in 20 control patients during the 5-year follow-up (RR for any event for the control group, 2.47; 95% CI, 1.48–4.20).</td>
</tr>
</tbody>
</table>

Note: CAD: coronary artery disease; 95% CI: confidence interval; RR: relative risk.
only group were not statistically significant among the women ($-7.3 \pm 18.9$ mg/dl) or the men ($-10.8 \pm 18.8$ mg/dl) when compared with controls. Because the NCEP step 2 diet failed to lower LDL-C levels in men or women with high-risk lipoprotein levels who did not engage in aerobic exercise, this finding highlights the importance of physical activity in the treatment of elevated LDL-C levels.

One possible conclusion is that losing weight is important in reducing LDL-C, independent of increased physical activity, for overweight men and postmenopausal women. For those with moderately elevated cholesterol levels, however, physical activity appears to be an important adjunct to a reduced-fat diet for increasing levels of HDL-C and reducing LDL-C.

Trials of weight loss and insulin resistance/diabetes.— The relative contributions of weight loss and aerobic exercise in reducing insulin resistance were compared in a trial (44) of 170 healthy, sedentary, obese, middle-aged and older men who were randomly assigned to a 9-month diet-induced weight loss intervention, a 9-month aerobic exercise training program, or weight maintenance. No weight loss was seen in the exercise-only group, compared with a 10% mean reduction in the weight-loss group. Weight loss decreased fasting glucose concentrations by 2%, insulin levels by 18%, and glucose and insulin areas during the oral glucose tolerance test (OGTT) by 8% and 26%, respectively. By contrast, aerobic exercise did not improve fasting glucose, insulin concentrations, or glucose responses during the OGTT, but did decrease insulin areas by 17% ($p < .001$). When compared with the control group, there was a significant decline ($p < .05$) in fasting glucose and insulin levels and in glucose areas in the intervention groups. Other similar trials have shown comparable findings.

A trial conducted in Da Qing, China, randomized 577 men and women with impaired glucose tolerance from 33 clinics into a control group, a diet-only group, an exercise-only group, and a diet-plus-exercise group. Randomization was conducted by clinic. Compared with the control group, the diet, exercise, and diet-plus-exercise groups experienced 31% ($p < .03$), 46% ($p < .0005$), and 42% ($p < .005$) lower risks of developing diabetes after 6 years, respectively. BMI did not appear to affect the results, with similar findings for subjects with BMIs less than 25 kg/m² and those with BMIs 25 kg/m² or greater (45).

Trials of weight loss among persons with previous CHD.— Several trials have been designed to test the association between weight loss, other lifestyle factors, and coronary atherosclerosis progression and clinical events among patients with CHD. The Stanford Coronary Risk Intervention Project (46) compared usual care with a multifactorial risk reduction approach (diet low in fat and cholesterol, exercise, weight loss, smoking cessation, and medications to favorably alter lipoprotein profile) among patients with atherosclerotic lesions defined by coronary angiography. Intensive intervention resulted in highly significant improvements in body weight (~4%) and lipid profile. Furthermore, the rate of narrowing of diseased coronary artery segments was 47% lower in the intervention group than in the usual-care group. Clinical cardiac events led to 25 hospitalizations in the risk-reduction group compared with 44 in the usual-care group (relative risk [RR], 0.61; 95% confidence interval [CI], 0.4 to 0.9). In the Lifestyle Heart Trial (47,48), performed among patients with angiography-defined coronary atherosclerosis, an experimental group (low-fat vegetarian diet, smoking cessation, stress management training, and moderate exercise) was compared with a usual-care control group for a one-year period. On average, coronary stenosis diameter regressed from 40.0% to 37.8% in the experimental group and progressed from 42.7% to 46.1% in the control group. Twenty-five cardiac events occurred in 28 experimental-group patients compared with 45 events in 20 control group patients during the 5-year follow-up (RR for the control group was 2.47; 95% CI, 1.48 to 4.20). These multifactorial trials were unable to assess the independent effect of weight loss or of other isolated lifestyle modifications and so have limited relevance for this panel.

Feasibility of Sustained CR for Weight Loss and Subsequent Maintenance

Given the current state of knowledge, is it feasible for humans to reduce their caloric intake over the long term? Several issues should be considered in answering this question. First, it is extremely difficult to get accurate assessments of dietary intake. Thus, a better answer to this question comes from studies that have asked participants to lose weight and maintain it, where weight is an objective measure. Such interventions, however, typically include not only CR but also increased exercise; as will be discussed, it appears that those who are successful at long-term weight loss use a combination of these strategies. Whether it is the combination of dietary restriction and increased exercise that is physiologically important, or whether adherence to both represents a marker of relatively heightened motivation and adherence to caloric restraint is unclear. Nevertheless, it does seem that those who adhere closely to both diet and exercise prescriptions do better in weight loss programs. Second, it should be noted that such data have been obtained on overweight participants who are intentionally attempting to lose weight. It is unclear whether similar effects would be observed in normal-weight persons.

Several large-scale hypertension trials have included weight loss as one of the interventions and carried out long-term follow-up. For example, the Trial of Nonpharmacologic Interventions in the Elderly is a newly completed randomized trial of sodium reduction and weight loss in older persons (aged 60 to 80) with SBP < 145 mm Hg and DBP < 85 mm Hg who were treated with a single antihypertensive medication. The 585 obese participants (mean BMI of 30 in men, 31.9 in women) were randomly assigned to sodium restriction, weight loss, the combination, or usual care. The intervention goal was to achieve and maintain a 4.5 kg (10 lb) or greater weight loss. The intervention included weekly meetings for an initial 4 months, biweekly meetings for the next 4 months, and monthly thereafter. A combination of small group and individual sessions were held; 89–93% of subjects assigned to the various conditions attended the final study visit (month 30). Subjects assigned to the weight loss-alone arm or the combined weight loss-plus-sodium restric-
tion arm achieved a mean weight loss of 5 kg (11 lb) at 6 months and maintained this through month 30. Subjects in the group assigned to the weight loss-alone group lost approximately 1 kg (2.2 lb) more than those in the combined weight loss-plus-sodium restriction group (40).

Similar positive long-term results for weight loss have been obtained in other hypertension clinical trials. For example, in the Treatment of Mild Hypertension Study, 902 participants aged 45 to 69 participated in a weight-loss intervention while also receiving antihypertensive medication or placebo. The intervention involved 6 months of intensive treatment, with a combination of group and individual sessions, and then individual sessions every 6–12 weeks for the remainder of the trial. Caloric intake was set at 1000–1200 kcal/day for women and 1400–1600 kcal/day for men, while the physical activity goal was to achieve an energy expenditure of 600 kcal/week. Participants lost a mean of 4.8 kg (10.5 lb) at 1 year, 3.09 kg (8.5 lb) at 2 years, 3.4 kg (7.4 lb) at 3 years, and 2.6 kg (5.7 lb) at 4 years. At the end of the study (year 4), 70% of participants weighed less than their baseline weight, while 34% maintained a weight loss of 4.5 kg (10 lb) or more (49). In the Trials of Hypertension Prevention, the weight loss intervention group lost a mean of 3.9 kg (8.6 lb) at 18 months, compared with the control group (50). No adverse effects of weight loss have been observed in any of these trials. Based on these as well as other trial data, it appears that weight loss can be achieved and maintained, at least over the short term (on the order of 1 to 3 years).

A key component of all of these interventions is continued contact and intensive treatment. As soon as treatment contact is reduced, participants tend to regain weight. Another strategy that may enhance weight loss in clinical trials of CR is the use of a controlled-feeding paradigm in which participants are given all or some of the food they should eat. This approach has been used recently in the ongoing Cardiovascular Risk Reduction Dietary Intervention Trial. In a study by Jeffery and colleagues (51), provision of food to subjects improved weight losses at 18 months. A study by Wadden and associates (52) prescribed a 925 kcal/day diet for 16 weeks that included a liquid formula diet four times a day and a frozen entree at dinner. After 16 weeks the participants consumed a 1200–1500 kcal/day diet. Weight losses for the diet-only group (no exercise) were 15.3 kg (33.7 lb) at the end of the 48-week program and 6.9 kg (15.2 lb) at the 1-year follow-up.

A further strategy to achieve weight loss is the use of medication, such as orlistat or sibutramine. In a recently published 2-year study of orlistat, subjects treated with placebo and a calorie-reduced diet maintained a loss of approximately 4 kg (8.8 lb) at 2 years, whereas those treated with orlistat three times a day (120 mg) and a calorie-restricted diet lost approximately 8 kg (17.6 lb) (53). Because orlistat is a gastrointestinal lipase inhibitor that reduces fat absorption by approximately 30%, it also had positive effects on LDL-C levels that were independent of the weight loss effect.

Finally, data from the National Weight Control Registry—a registry of persons who have lost at least 13.6 kg (30 lb) and kept the weight off for at least one year—provide some information regarding long-term weight loss. These data, however, are based on self-report, and the registry does not include a “control” population of those unsuccessful in their weight-loss endeavors. There are currently more than 2,500 individuals in the registry who have been extremely successful in their weight loss efforts, far exceeding the minimum criteria for entry. On average, participants have lost more than 27.2 kg (60 lb) and kept them off for more than 6 years and have reduced their BMIs from 35 to 24.5 kg/m². Ninety percent report that they used a combination of diet plus exercise to lose weight, and a similar percentage report that this combination is also used for maintenance. In this registry, current dietary intake is assessed using the Block Food Frequency Questionnaire and activity using the Paffenbarger Physical Activity Questionnaire. The average diet reported by registry members contains 1380 cal/day with 24% of calories from fat, 19% from protein, and 56% from carbohydrates. Perhaps of greater interest is their level of self-reported exercise. These participants report a mean energy expenditure of more than 2800 cal/week, with 52% of participants exceeding a level of 2000 kcal/week. A large percentage of their expenditure (28%) comes from high-intensity physical activity such as running, jogging, step aerobics, or weight-lifting.

RECOMMENDATIONS FOR RESEARCH

Studies in Nonprimates
Not applicable.

Studies in Nonhuman Primates
Not applicable.

Studies in Humans

Patterns of weight change with age.—We have few data on longitudinal patterns of weight change over time, especially among minority populations. Some of these minority populations also are those in which the prevalence of overweight is highest. Understanding patterns of weight change over time may allow us to identify critical periods for emphasizing prevention of weight gain, because we have little success currently with long-term maintenance of weight loss. Existing databases (e.g., military databases) can help provide information.

Caloric restriction and morbidity/mortality.—One phenotype associated with caloric restriction in animals is not gaining weight after early adulthood, excluding pregnancy. We recommend testing the hypotheses that CR in humans, defined using this phenotype, is associated with lower morbidity and greater longevity. Such a study can be accomplished by identifying subgroups of individuals who have not gained weight since early adulthood from existing cohorts (e.g., the Aerobics Center Longitudinal Study, the Framingham Heart Study, the Harvard Alumni Health Study, the Health Professionals’ Follow-up Study, the Honolulu Heart Study, the Iowa Women’s Health Study, the Nurses’ Health Study, the Seventh Day Adventist Study, etc.) and following them over time for mortality. While individual cohorts are unlikely to have large numbers of persons with this phenotype, pooling sub-
jects from different cohorts will likely provide sizable numbers of individuals on whom the hypotheses can be tested.

Again, we acknowledge that one of the limitations of this phenotype is that different individuals achieve lifetime weight stability through various means, and weight stability may not necessarily be due to low levels of caloric intake. We recommend identifying a group that maintains stable weight by eating fewer calories than the average person, as well as another group that may actually consume more calories than average but balances the intake with higher energy expenditure. The morbidity/mortality experience of these two groups then can be compared.

Further, while mortality is an important endpoint, it also is important to determine whether individuals are living longer free of chronic diseases and/or disability. Thus, we need to assess physical and mental function in these individuals.

We further propose that subsequent studies explore the most relevant aspects resulting in this phenotype in humans (i.e., is the phenotype the result of decreased caloric intake relative to “average”? Is it increased energy expenditure relative to “average”? Is it genetically determined?). Subgroups of subjects from the large group could be invited to participate in more detailed examination and testing (e.g., using doubly labeled water and such).

Voluntary weight loss and morbidity/mortality.—We could test further in prospective observational studies the hypothesis that voluntary weight loss does not increase (and may decrease) the risk of chronic disease or death. This would require the development of valid instruments to assess involuntary/voluntary weight loss. However, it would be difficult to develop such instruments and to avoid selection biases related to which individuals lose weight.

Another unresolved issue is whether weight change may have different effects on morbidity and/or mortality depending on when the weight change occurs. In the Honolulu Heart Study, weight gain early in life was associated with increased risk of coronary heart disease; in contrast, weight gain later in life was associated with increased risk (54).

Optimal body weight.—We could more fully test the hypothesis that, in a population of initially nonsmoking healthy people, being thin carries a lower risk of disease and increases longevity compared with being average weight. Comparisons with animal data would be facilitated if investigators would provide survival curves associated with different levels of body weight. However, while these curves might reveal whether lower body weights are associated with greater median survival (assuming biases and confounding have been controlled), they will not help identify whether life span has been increased. Unlike animal models, we do not have good data regarding what the maximal life span might be in different populations of humans.

Long-term effects of weight loss medications.—Preliminary data suggest that weight loss medications such as orlistat or sibutramine are effective in helping subjects achieve greater weight loss. Because such drugs are new, there are no long-term data regarding potential side effects. It would be important to continue follow-up over the long term of subjects who have taken such medications.

Prevention of weight gain.—Because we do not appear to have much success in getting those who are overweight to maintain weight loss over the long term, it is important to put emphasis on developing methods and policies to prevent weight gain in the first place.

Issues related to diet and exercise.—Finally, other crucial research would include: comparative studies examining gender, ethnicity, age, and socioeconomic status to disclose biological differences and, equally important, to identify some of the barriers to adopting new lifestyles; studies evaluating the relative impacts on cardiovascular risk of isocaloric, low-fat diets, and hypocaloric diets among both lean and overweight people with mild-to-moderate levels of hypercholesterolemia; assessing the role of subtypes of fat, dietary glycemic index, and dietary fiber on vascular risk factors; establishing the importance of the frequency and size of meals, two factors that influence insulin resistance; and investigating the frequency and intensity of exercise in terms of their relationship with blood pressure, lipid levels, and carbohydrate metabolism.

Recommendations on Methodologic Approaches

Improved measurements of caloric intake and energy expenditure.—Because of the imprecision involved in measuring caloric intake and energy expenditure, studies have often used weight loss as a more objective measure. Better instruments are needed to measure both these parameters; further, these instruments need to be practical and made available for use in epidemiologic studies where large numbers of subjects are likely to be involved. Special attention should be given to developing and validating methods to assess diet and physical activity over the adult years that will characterize patterns of diet and physical activity over this period. This will then enable categorizing the phenotype of individuals who remain weight stable over most of their adult years into those who achieve this phenotype by decreasing caloric intake and those who may balance a higher caloric intake with greater physical activity.

Development of better weight reduction techniques.—Another important avenue of exploration is the development of weight reduction methods, including pharmaceutical interventions, with higher levels of effectiveness. Many weight loss trials have high drop-out rates in both intervention and control arms. Improving compliance over long periods is a challenge that must be pursued using self-motivation and other psychological intervention tools.

Use of surrogate endpoints for the aging process.—We need to develop better surrogate endpoints for the aging process. Atherosclerosis may not be a good marker, as the prevalence of atherosclerosis is low in some populations of older individuals. Among the surrogate endpoints that might be appropriate for investigation are renal function (e.g., glomerular filtration rate), vascular stiffness, oxidative stress, glycation products, levels of interleukin-6, or tumor necrosis factor alpha. (Further details are provided in the reports of other panels.)
Recommendations Regarding Resources and Infrastructure

It would be valuable to continue funding for existing cohorts of subjects in large epidemiologic studies where information has been gathered on weight, weight loss, and individuality of weight loss. This will allow some of the gaps outlined above to be addressed. Since most existing cohorts tend to be predominantly white, large cohorts of minorities with high rates of follow-up should be encouraged.

As proposed above, we recommend a pooling project bringing together subjects from longstanding cohort studies to test the hypotheses that one phenotype of caloric restriction in humans—not gaining weight after early adulthood, excluding pregnancy—is associated with lower morbidity and greater longevity. If the data support this hypothesis, these subjects also should be studied to determine which aspects resulting in the phenotype (intake, expenditure, genetics) are most relevant in humans.

Acknowledgments

We thank Pat Skerret for his expert editorial assistance.

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References

26. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood


Appendix A

Notes for Appendix Figures 1A–4A

Subjects for these analyses were men and women participating in the Aerobics Center Longitudinal Study (1). They are a subgroup of the total population who completed two examinations at the Cooper Clinic, Dallas, TX. All reported their weight at age 21 in response to a question on the medical history questionnaire: “What was your weight at age 21?” Other data from the examination included measured weights at the first (mean age, 44 years; range 30–73 years for men, 30–72 years for women) and second examinations (mean age, 49 years), and responses to questions on the medical history questionnaire about physical activity. Physical activity was assessed by a series of questions about participation in leisure-time physical activities. The emphasis was on sports play and fitness activities. Those who reported no participation in any physical activity in the 3 months prior to the examination were classified as inactive; all others were classified as active. This is a crude and imprecise classification, but previous work indicates that it has some validity. Figures 1A and 2A show the average weights at three timepoints for individuals in quantiles of weight at age 21. Study participants were assigned to a weight quantile at age 21 and remained in that same quantile as their mean weight was tracked at the first and second examinations. The highest and lowest quantiles are shown.
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- How often are you dieting (eating less than you would like)?
  - Never
  - Rarely
  - Sometimes
  - Often
  - Always

The never and rarely categories were combined to create the “rare” category, and the often and always categories were combined to create the “often” category. Study participants were assigned to the dieting frequency category based on responses at their first examination, and they remained in these respective categories for age 21 and at the first and second follow-up examinations.

**Figure 4A.** Patterns of weight change with age according to weight and physical activity categories, 1,112 women, Aerobics Center Longitudinal Study.

**Figure 5A.** Lifetime weight patterns based on percentile distributions, Harvard Alumni Health Study. Data based on 6,175 men who had a physical examination at age 18 and who also returned questionnaires in 1962/1966, 1977, 1988, and 1993, with known data on weight.

**Figure 6A.** Lifetime weight patterns based on percentile distributions, Honolulu Heart Study. Data based on 3,611 Japanese American men. Weight was measured at Examination 1 (1965–1968) and Examination 4 (1992–1994); weight at age 25 was reported at Examination 1.

**REFERENCE**

1. Blair SN. Aerobics Center Longitudinal Study. Paper presented at: Caloric Restriction Clinical Implications Advisory Group; March 8–10, 1999; Bethesda, MD.

**Appendix B**

**Notes for Text Figures 1 and 2**

Subjects for these analyses were men and women participating in the Aerobics Center Longitudinal Study (1). They are a subgroup of the total population who completed two examinations at the Cooper Clinic, Dallas, TX. All reported their weight at age 21 in response to a question on the medical history questionnaire: “What was your weight at age 21?” Other data from the examination included measured weights at the first (mean age, 44 years; range 30–73 years for men, 30–72 years for women) and second examinations (mean age, 49 years), and responses to questions on the medical history questionnaire about physical activity and dietary practices. The specific question on dieting and the response categories were:

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