Effect of weight on cardiovascular disease$^{1-3}$

William B Kannel, Ralph B D'Agostino, and Janet L Cobb

ABSTRACT  
Involuntary weight gains worsen all elements of the cardiovascular risk profile, including dyslipidemia, hypertension, insulin-resistant glucose intolerance, left-ventricular hypertrophy, hyperuricemia, and elevated fibrinogen. On the basis of data from the Framingham Heart Study and from other studies, it can be concluded that the degree of overweight is related to the rate of development of cardiovascular disease. After 26 y of follow-up in the Framingham study, each SD increment in relative weight was associated with 15% and 22% increases in cardiovascular events in men and women, respectively. Avoidance of weight gain after the age of 25 y is advisable to reduce cardiovascular mortality. There is a great potential benefit to weight loss, suggesting that weight control as a means for preventing and lessening cardiovascular disease become a national health priority. The optimal weight for avoidance of cardiovascular disease and prolonging life corresponds to a body mass index of 22.6 for men and 21.1 for women.  

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KEY WORDS  
Cardiovascular disease, obesity, weight

INTRODUCTION

Overweight carries a penalty in that it leads to a worsening of all the elements of the cardiovascular risk profile, including dyslipidemia, hypertension, insulin-resistant glucose intolerance, left-ventricular hypertrophy, hyperuricemia, and elevated fibrinogen. Largely as a consequence of these factors, overweight is associated with excess occurrence of cardiovascular events (1,2). The abdominal pattern of body fat appears to be the most hazardous; weight fluctuations, as a result of repeated unsuccessful attempts to achieve sustained weight loss, further accelerate atherogenesis.

We attempt to provide insights from the Framingham Study and elsewhere about the effect of weight gain and weight overweight on the occurrence of cardiovascular disease and the risk factors that promote it. We also examine the effect of weight fluctuation and the influence of weight reduction.

RISK FACTOR BURDEN

The association of adiposity with cardiovascular risk factors is well established (1,2). However classified, the burden of major risk factors is substantially greater in overweight [body mass index (BMI) $\geq 27$] than in lean individuals (BMI $\leq 22$) (Table 1) (2). Systolic and diastolic blood pressures are higher, serum total cholesterol is increased, and concentrations of sugar in the blood are moderately greater. Furthermore, there is a strong continuous graded relation so that the greater the degree of adiposity, the greater the level of the risk factors. Low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol are also adversely affected by increased adiposity in a linear fashion (3).

In addition, it was shown many years ago in the Framingham Study that changes in weight are mirrored by corresponding changes in blood pressure, serum cholesterol, uric acid, and blood sugar (4). More recent data from the Framingham Study continue to show improvement in blood pressure and cholesterol with weight loss in both the general and healthy population (Table 2).

Overweight has been shown to be a major determinant of hypertension in the general population. In the Framingham Offspring Study, 40–70% of newly developing essential hypertension could be attributable to overweight, defined by a BMI $\geq 23$ or a subscapular skinfold thickness of $\geq 1$ cm (5). Overweight has also been shown to be a powerful determinant of the occurrence of non-insulin-dependent diabetes mellitus in the general population (6). In the Framingham Study cohort, each SD increment in relative weight was associated with 46% and 61% increases in the risk of developing diabetes in men and women, respectively (6). Only a high-normal concentration of sugar in the blood rivaled this effect.

There appears to be a biologically plausible metabolic basis for risk factors to be influenced by weight and weight gain. Abdominal adiposity has been shown to be related to insulin resistance (7,8), and weight loss improves insulin resistance (9). Insulin resistance and hyperinsulinemia are associated with lipoprotein-lipase deficiency, which causes triacylglycerols to be elevated and HDL to be reduced. Increased reabsorption of sodium occurs as a result of hyperinsulinemia, which expands the blood volume and promotes hypertension. Insulin resistance eventually produces enough glucose intolerance to result in frank diabetes. All these effects of abdominal adiposity accelerate atherogenesis (Figure 1).

CARDIOVASCULAR HAZARDS

Considering the foregoing, it is not surprising that overweight has been associated with an increased rate of occurrence

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1 From the Department of Medicine, Section of Preventive Medicine and Epidemiology, and the Department of Mathematics, Boston University, Framingham Heart Study, Framingham, MA.

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3 Reprints not available. Address correspondence to WB Kannel, Boston University, Framingham Heart Study, 5 Thayer Street, Framingham, MA 01701.
TABLE 1  
Average risk factor values in lean compared with obese persons with stable weights over 6 y

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Lean</th>
<th></th>
<th>Obese</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>(n = 77)</td>
<td>n = 255)</td>
<td>(n = 281)</td>
<td>(n = 228)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129</td>
<td>125</td>
<td>139</td>
<td>145</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80</td>
<td>79</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Cigarettes (no./day)</td>
<td>18</td>
<td>11</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.97</td>
<td>6.26</td>
<td>6.49</td>
<td>6.62</td>
</tr>
<tr>
<td>Blood sugar (mmol/L)</td>
<td>4.3</td>
<td>4.4</td>
<td>4.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

1 Subjects from the Framingham Study, and aged 35–59 y. Subjects were weight-stable within 2.3 kg (5 lb). Risk factors adjusted for age. Lean = BMI ≤ 22; obese = BMI ≥ 27. BP, blood pressure.

The influence of the subscapular skinfold thickness on coronary heart disease (CHD) incidence appears to be greater than the effect of BMI, although each appears to have an independent effect (Table 3). Regional obesity has been examined in the Framingham cohort in relation to cardiovascular events. Multivariate analysis, taking all the major cardiovascular risk factors into account, indicated an independent effect of abdominal adiposity on stroke, CHD, cardiovascular, and all-cause mortality in men. In women, only the ratio of subscapular to triceps skinfold thickness was found to contribute independently to CHD, cardiovascular, and all-cause mortality (2,11). Thus, regional obesity appears to be an independent contributor to cardiovascular disease at a given level of general obesity; its effect is only partially mediated through promotion of other major risk factors. However, comprehensive review of all relevant data indicates that cardiovascular disease is probably as closely related to general obesity as to abdominal obesity.

TABLE 2  
Mean risk factors achieved by weight change in the total population compared with a healthy population

<table>
<thead>
<tr>
<th>Mean risk factor</th>
<th>Total population</th>
<th>Healthy population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lost</td>
<td>Stable</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>130</td>
<td>132</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>Cigarettes (no./day)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.13</td>
<td>6.32</td>
</tr>
<tr>
<td>Blood sugar (mmol/L)</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>BMI</td>
<td>25</td>
<td>26</td>
</tr>
</tbody>
</table>

1 Subjects were men aged 35–49 y from the Framingham Study and with a weight change of ≥ 2.3 kg (5 lb). Risk factor values are adjusted for age, risk factor at initial exam, and BMI achieved. Healthy = free from diabetes, high blood pressure, and cardiovascular disease. SBP, systolic blood pressure; DBP, diastolic blood pressure.

2 Significantly different from subjects who lost weight or remained weight-stable, P < 0.001.

3 Significantly different from subjects who lost weight or remained weight-stable, P < 0.01.

TABLE 3  
Risk of coronary heart disease by body mass index and subscapular skinfold thickness

<table>
<thead>
<tr>
<th>Subscapular skinfold thickness</th>
<th>Lowest (2–12 mm)</th>
<th>Middle (13–19 mm)</th>
<th>Highest (20–51 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile of BMI</td>
<td>Lowest (14–22)</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Middle (23–25)</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Top (26–40)</td>
<td>46</td>
<td>72</td>
</tr>
</tbody>
</table>

1 Age-adjusted 12-y rate per 1000; from the Framingham Study.

In the long term, amount of weight gained after the age of 25 y (or on completion of musculoskeletal growth) carries a distinct penalty of cardiovascular disease that is proportional to the amount of weight gained (12). Those who throughout 26 y of follow-up lost > 10% of their weight at 25 y had a moderately lower risk than did those whose weight remained stable. Those who gained weight over what they weighed at the age of 25 y increased their risk in proportion to the amount of weight gained.

WEIGHT CHANGE AND ALL-CAUSE MORTALITY

It is commonly assumed that voluntary weight loss by overweight individuals is beneficial, whereas involuntary weight loss often reflects serious disease. The Framingham Study investigated variability in body weight over eight biennial exams in relation to total mortality, CHD mortality and morbidity, and development of cancer. Persons with highly variable body weights had increased total mortality and CHD mortality and an excess of CHD events (13). Through the use of multivariate analysis, which also controlled for obesity, trends in weight over time, and coexistent cardiovascular risk factors, it was found that the association between weight fluctuations and the endpoints persisted with increased relative risks for those with substantial weight fluctuation (3). It was concluded that fluctuations in body weight may have negative health consequences. It is difficult, however, for epidemiologic studies to adequately control for all the possible confounders, thus making the conclusions somewhat speculative (14).

A review of reports analyzing long-term weight change in relation to all-cause mortality found that mild to moderate weight gains were generally associated with the lowest all-cause mortality. Weight loss was generally associated with the highest mortality. Those with the greatest weight gains typically had a somewhat higher mortality (5). These data agree with those of the Framingham Study when the whole population sample is taken into consideration. However, when weight
fluctuation is examined separately in obese and lean persons, it is evident that only in lean persons is weight loss associated with excess mortality (Table 4). It thus appears that only involuntary weight loss is associated with excess mortality.

OPTIMAL WEIGHT

The optimal weight for survival and avoidance of weight-related cardiovascular disease is difficult to specify. Data from the American Cancer Society and from studies by insurance companies are most relevant because such data are confined to the middle class, a population group without health impairments or confounding resulting from low socioeconomic status, and can be used to explore the effect of weight in non-smokers. These data suggest that the lowest mortality occurs in persons who are slightly underweight (16). The insurance data did indicate some excess mortality in those who were underweight, but this declined with time in contrast with mortality in overweight persons, which increased with time. Whether optimal weights vary by age is a matter of dispute (17). This determination is confounded by cigarette smoking (18), by an influence of occult illness on weight, and by the fact that most of the reduced weight in the elderly is not characteristic of their lifetime weight pattern and usually reflects involuntary weight loss later in life.

It may be best to define optimal weight for avoidance of cardiovascular disease as that weight that optimizes the cardiovascular risk profile (3). By this criterion, a healthy body weight would correspond to a BMI (in kg/m²) of 22.6 in men and 21.1 in women and a subscapular skinfold thickness < 12 mm in men and < 15 mm in women (3).

It is estimated from Framingham Study data that, if every person maintained his or her optimal weight, there would be 25% less CHD and 35% fewer strokes or episodes of cardiac failure. Judging from the effect of weight loss on atherogenic risk factors, one would expect a 20% reduction of weight in obese persons to confer a 40% reduction in chances of developing coronary heart disease (19). Considering that obesity is the most prevalent metabolic disorder in affluent societies, there is much to be gained by curbing unnecessary weight gain.

PREVENTIVE IMPLICATIONS

Evaluation of the possible benefits and adverse effects of weight loss is difficult without random assignment to weight loss in a controlled trial. Until better methods are developed for achieving sustained weight loss, such trials are not feasible. Observational epidemiologic investigation can only attempt to show guilt by association. Voluntary and involuntary weight loss and weight gain occur in the general population for a variety of reasons, making it difficult to separate benefits from adverse effects and causes from consequences. Data from the Framingham Study and other epidemiologic investigations have, however, provided useful insights from repeated weight determinations in population samples, assessment of patterns of obesity, and evaluation of corresponding changes in cardiovascular risk factors and overall cardiovascular mortality (3–6, 11–13).

The usual state of affairs in most affluent societies is for weight to be gained with advancing age and once put on to be tenaciously kept. The history of attempts at weight control is one of repeated unsuccessful attempts. Sustained weight loss is, therefore, usually unintentional. This makes it difficult to evaluate from observational studies the benefits of weight reduction in obese persons who have an indication for prescribed weight loss.

However, on the basis of demonstrated benefits of weight loss and adverse metabolic effects of weight gain on cardiovascular risk factors, there is a powerful rationale for advocating avoidance of overweight and prompt correction of weight gain of > 2.3–4.5 kg (5–10 lb). The potential benefit of this recommendation is significant in reduced mortality and morbidity associated with cardiovascular disease. No other risk factor correction influences as powerfully the cardiovascular risk profile, affecting blood lipids, blood pressure, glucose tolerance, and left-ventricular hypertrophy, leading to improved long-term health (2,20).

SUMMARY

Adiposity carries a penalty of an adverse cardiovascular risk profile. The greater the degree of overweight, the higher the blood pressure, insulin resistance, triacylglycerol, and ratio of total to HDL cholesterol. Largely as a result of these metabolic effects, overweight is associated with increased occurrence of coronary and stroke events. Each SD in relative weight gain confers 15% and 22% increases in cardiovascular disease in men and women, respectively.

Highly variable weights, often reflecting repeated unsuccessful attempts at weight reduction, may be associated with increased coronary risk. Weight loss, despite improvement in risk factors, has been erroneously reported to be associated with excess overall mortality. In the Framingham study, only involuntary weight loss in lean persons was associated with excess mortality.

Avoidance of weight gain after the age of 25 y is a rational means for reducing the annual toll of cardiovascular mortality. Weight control is a logical first approach to control mild to moderate hypertension, dyslipidemia, glucose intolerance, hy-

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**TABLE 4**

Age-adjusted relative risk for cumulative total mortality by weight change

<table>
<thead>
<tr>
<th>Weight change (exams 4–7)</th>
<th>Total population</th>
<th>Obese population</th>
<th>Lean population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 2016)</td>
<td>Women (n = 2634)</td>
<td>Men (n = 791)</td>
</tr>
<tr>
<td>Losers of ≥ 2.3 kg</td>
<td>1.22&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.23&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.05</td>
</tr>
<tr>
<td>Stable</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Gainers of ≥ 2.3 kg</td>
<td>1.06</td>
<td>1.06</td>
<td>0.87</td>
</tr>
</tbody>
</table>


<sup>2</sup> Significantly different from stable weight, P < 0.05
peruricemia, and left-ventricular hypertrophy. There is a sound rationale to making weight control a high priority for preventing cardiovascular disease and lessening the severity of disease once initiated.

On the basis of estimates drawn from the Framingham Study, if every person maintained his or her optimal weight, there would be a 25% reduction in CHD and 35% fewer strokes or episodes of cardiac failure. Considering the prevalence of overweight individuals in the United States, there is much to be achieved by working to prevent adult weight gain and to reduce body weight in those who are already overweight.

The optimal weight for avoidance of cardiovascular disease and prolonging life corresponds to a BMI of 22.6 for men and 21.1 for women or a subscapular skinfold thickness < 12 mm in men and < 15 mm in women.

REFERENCES