Obesity as an Independent Risk Factor for Cardiovascular Disease: A 26-year Follow-up of Participants in the Framingham Heart Study

HELEN B. HUBERT, M.P.H., PH.D., MANNING FEINLEIB, M.D., DR.P.H., PATRICIA M. MCNAMARA, AND WILLIAM P. CASTELLI, M.D.

SUMMARY The relationship between the degree of obesity and the incidence of cardiovascular disease (CVD) was reexamined in the 5209 men and women of the original Framingham cohort. Recent observations of disease occurrence over 26 years indicate that obesity, measured by Metropolitan Relative Weight, was a significant independent predictor of CVD, particularly among women. Multiple logistic regression analyses showed that Metropolitan Relative Weight, or percentage of desirable weight, on initial examination predicted 26-year incidence of coronary disease (both angina and coronary disease other than angina), coronary death and congestive heart failure in men independent of age, cholesterol, systolic blood pressure, cigarettes, left ventricular hypertrophy and glucose intolerance. Relative weight in women was also positively and independently associated with coronary disease, stroke, congestive failure, and coronary and CVD death. These data further show that weight gain after the young adult years conveyed an increased risk of CVD in both sexes that could not be attributed either to the initial weight or the levels of the risk factors that may have resulted from weight gain. Intervention in obesity, in addition to the well established risk factors, appears to be an advisable goal in the primary prevention of CVD.

THE IMPORTANCE of body weight, body mass and other measures of adiposity in the prediction of cardiovascular disease (CVD) has been the subject of longstanding debate. Many studies have shown that the incidence of certain types of CVD, particularly coronary heart disease and stroke, is greater in heavier persons, but only a few suggest that any obesity index makes an additional contribution to risk once the levels of coexisting risk factors are taken into account. Obesity is associated with elevated blood pressure, blood lipids and blood glucose, and changes in body weight are coincident with changes in these risk factors for disease. Thus, the consensus has been that the increased risk among heavier persons is due primarily to the influence of the associated risk factor profile and not to the degree of obesity per se. The existing data have also been interpreted to suggest that obesity is benign when it exists without other major risk factors for CVD.

In this report, we reexamine the obesity question and describe the influence of relative weight on the 26-year incidence of CVD in Framingham men and women. Earlier results from this study suggested that the degree of obesity is not a potent independent risk factor for CVD in general, particularly among women. However, these conclusions were based on analyses of the influence of relative weight over shorter periods of follow-up and may not have conveyed the true impact of disease risk.

Such a reevaluation appears timely in view of the current revisions to the original Metropolitan Life Insurance Company desirable weight tables. These desirable weights, derived from the mortality experiences of subscribers, have been revised upward because new data on insured lives suggest that it is healthier to be heavier than once thought. Recent analyses of long-term mortality in Framingham indicate, however, that this may not be so; minimal mortality occurs at previously published levels of desirable weight. Although recent statistics indicate that the general U.S. population, particularly men, has been getting heavier over the last few decades, considerably more data are needed to evaluate the implications of this trend. Likewise, revisions to the desirable weight tables seem premature, because the complex relationships between body weight and health or disease are so poorly understood. This reappraisal of the impact of relative weight on cardiovascular morbidity in Framingham further emphasizes the need for caution, because health-related issues other than total mortality should be considered in arriving at acceptable levels of desirable weight.

Methods

The Framingham Heart Study population has been examined and followed biennially for the development of CVD since 1948. In this report we present the morbidity experience of 2252 men and 2818 women, ages 28–62 years, who were free of clinically recognizable CVD at the first study examination, which took place between 1949 and 1950. Manifestations of CVD included coronary heart disease, congestive heart failure, stroke and intermittent claudication.

For the purposes of this report, the subjects were classified by weight and other risk attributes at the initial examination only and observed over 26 years for the development of CVD. The obesity index chosen to characterize the population was Metropolitan Relative Weight (MRW), or percentage of desirable weight (the ratio of actual weight to desirable weight × 100). Desirable weight for each sex was derived from the...
1959 Metropolitan Life Insurance Company tables by taking the midpoint of the weight range for the medium build at a specified height. Since desirable weights were reported for subjects wearing both clothes and shoes, these figures were adjusted in order to apply them to Framingham subjects, who were weighed and measured in a dressing gown and without shoes (table 1).

Other characteristics of interest at the initial examination were systolic blood pressure, measured in the left arm of the seated subjects with a mercury sphygmomanometer and a 14-cm cuff long enough to fit the most obese arm; serum cholesterol concentration, determined by the method of Sperry; the number of cigarettes smoked per day, assessed by a physician-administered medical history questionnaire; glucose intolerance, defined by a casual blood glucose level of at least 120 mg%, the presence of glycosuria or a definite history of diabetes; and left ventricular hypertrophy on a 13-lead ECG.

Criteria for each cardiovascular outcome during follow-up were standardized and decisions regarding diagnosis were made by a panel of Framingham investigators. Coronary heart disease included diagnoses of (1) angina pectoris, evidenced by a typical history of chest pain on a physician-administered questionnaire; (2) myocardial infarction, determined by specified electrocardiographic changes, diagnostic elevation of serum enzymes with prolonged ischemic chest pain, or autopsy; (3) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on the ECG; and (4) sudden (less than 1 hour) or nonsudden coronary death. Congestive heart failure was indicated when at least two major or one major and two minor diagnostic conditions existed concurrently upon examination. The major stroke end point of interest was atherothrombotic brain infarction, defined as the sudden onset of a localizing neurologic deficit lasting over 24 hours without evidence of embolism or hemorrhage. Intermittent claudication was diagnosed from subjective responses to questions on calf cramping during exertion.

Preliminary analyses of the data consisted of calculating crude incidence rates of disease by level of MRW. More formal statistical methods used to assess the influence of MRW independently of the coexisting levels of the major cardiovascular risk factors relied upon multivariate logistic regression procedures in which the probability of an event was described as a function of several attributes measured at entry to the Framingham Study. Regression coefficients generated by the logistic model measured the strength of the association between adiposity and the probability of disease after adjustment for age and the other risk factors. The coefficients divided by their standard errors provided tests of significance to indicate whether these relationships were significantly different from zero ($p \leq 0.05$ when $z \geq 1.96$). Standardized coefficients that adjust for differences in measurement units between variables were also calculated to show the impact of weight relative to the other risk factors for disease.

Results

During the 26-year follow-up, 870 men and 688 women developed clinically recognizable CVD. Although some subjects had more than one manifestation of disease, coronary heart disease accounted for a large proportion of the events, 75% and 66% in men and women, respectively. Congestive failure occurred in 183 men and 165 women and atherothrombotic stroke in 106 men and 103 women. Intermittent claudication was diagnosed more often in males than in females (171 vs 112).

At entry to the study, the disease-free Framingham cohort appeared to be considerably overweight. On the average, men were 18.9% and women 20.5% above desirable weight. Although the distributions of initial relative weights were very similar in men younger than 40 years, 40–49 years and 50 years or older, women appeared to be heavier in each subsequent age group (fig. 1). Clearly, a larger proportion of females than males were at the upper end of the weight distribution, particularly among the 50–62-year-olds.

Figure 2 shows sex- and age-specific crude incidence rates for total CVD over 26 years by MRW at entry to the study. For this purpose only, relative weight was categorized as less than 110, 110–129, and 130 or over; the middle category spanned evenly over the mean weights for men and women. The risk of CVD increased in both men and women with increasing MRW. However, the association of weight to inci-

### Table 1. Adjusted Desirable Weights for the Framingham Heart Study Participants

<table>
<thead>
<tr>
<th>Height (inches)</th>
<th>Weight (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>55</td>
<td>94</td>
</tr>
<tr>
<td>56</td>
<td>97</td>
</tr>
<tr>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td>58</td>
<td>103</td>
</tr>
<tr>
<td>59</td>
<td>106</td>
</tr>
<tr>
<td>60</td>
<td>116</td>
</tr>
<tr>
<td>61</td>
<td>119</td>
</tr>
<tr>
<td>62</td>
<td>122</td>
</tr>
<tr>
<td>63</td>
<td>125</td>
</tr>
<tr>
<td>64</td>
<td>128</td>
</tr>
<tr>
<td>65</td>
<td>131</td>
</tr>
<tr>
<td>66</td>
<td>135</td>
</tr>
<tr>
<td>67</td>
<td>140</td>
</tr>
<tr>
<td>68</td>
<td>144</td>
</tr>
<tr>
<td>69</td>
<td>148</td>
</tr>
<tr>
<td>70</td>
<td>152</td>
</tr>
<tr>
<td>71</td>
<td>157</td>
</tr>
<tr>
<td>72</td>
<td>161</td>
</tr>
<tr>
<td>73</td>
<td>166</td>
</tr>
<tr>
<td>74</td>
<td>170</td>
</tr>
</tbody>
</table>
Similar relationships were evident between MRW and coronary disease, the most frequent manifestation of CVD (fig. 3). Incidence also increased with increasing MRW, and the gradient of risk was steeper in the younger men and women. Among men younger than 50 years, the heaviest group experienced twice the risk of coronary disease compared with the leanest group. The risk was increased 2.4-fold among obese women of similar age. The relationships for risk of myocardial infarction were similar to those for total coronary disease (fig. 4). However, there was a much stronger gradient of risk for sudden death with increasing MRW in each age group in both sexes (fig. 5). In fact, these crude rates suggest that the impact of weight on risk may be most pronounced for this outcome. Figure 6 shows that the 26-year incidence of congestive heart failure in the younger men and women increased 2.5- to 3-fold from the leanest to the heaviest subjects. Unlike coronary disease, it appeared that the risk of congestive failure in women was elevated only in the most obese group. MRW had a greater impact on the incidence of atherothrombotic stroke in women than in men (fig. 7). Women younger than 70 years who were 30% or more over desirable weight experienced over four times the stroke rate of the leanest group.

However, not every cardiovascular end point was consistently related to MRW. The 26-year incidence of intermittent claudication, indicative of peripheral vascular disease, did not appear to be clearly related to the degree of overweight in either men or women (fig. 8). Multivariate logistic regression analyses were undertaken to ascertain whether the strong relationships between weight and disease would persist upon adjustment for the influence of the coexisting levels of the major CVD risk factors. These included age, systolic blood pressure, serum cholesterol, cigarettes per day,
glucose intolerance (no, yes), and electrocardiographic left ventricular hypertrophy (no, possible, definite). In all regression procedures, MRW and age were entered as continuous rather than categorical variables. The results in table 2 indicate that MRW was a significant predictor of total CVD in both men and women after adjustment for risk factors. Although independent relationships were apparent for angina, coronary disease other than angina, congestive failure, and coronary death in both sexes, the probabilities of myocardial infarction, atherothrombotic stroke, and cardiovascular death were associated with the degree of obesity in women only. (The regressions that adjusted for age alone yielded statistically significant associations between all end points and obesity in both sexes.) MRW was clearly a strong predictor of sudden death in males. The fact that MRW was not significantly associated with sudden death in females could be attributed to the small number of events in this group. The coefficients in table 2 suggest that the strength of the association was greatest for sudden death in men and congestive failure in women and that the relationship between MRW and coronary disease was stronger in males than in females because of the greater influence of this characteristic on the development of angina in men. Inclusion of additional risk factors (cardiac enlargement, heart rate and vital capacity) in the regression for congestive failure did not alter the relationship between weight and disease. Although it has been suggested that lean compared to obese hypertensives may be at increased risk of death over 8 years of follow-up in Framingham (unpublished data), further analyses of 26-year incidence of CVD and coronary death presented no evidence to indicate

Figure 3. Twenty-six-year incidence of coronary heart disease by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.

Figure 4. Twenty-six-year incidence of myocardial infarction by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.

Figure 5. Twenty-six-year incidence of sudden death by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.
that there was such an interaction effect between weight and its strongest correlate, blood pressure.

The magnitude of the standardized regression coefficients indicated that degree of obesity was one of the best predictors of total CVD in women (table 3). In this group, weight ranked only behind age and blood pressure, while in men it ranked behind all the other risk factors. MRW among males was a better predictor of manifestations of coronary heart disease than blood pressure, cigarette smoking, glucose intolerance or electrocardiographic left ventricular hypertrophy.

It has been argued that obesity does not convey an increased risk of disease unless it is accompanied by elevations in such characteristics as blood pressure or blood lipids. This hypothesis was examined by calculating CVD incidence rates by level of MRW in men and women younger than 50 years of age who were free of risk factors at entry into the study (fig. 9). That is, they were normotensive, had serum cholesterol levels less than 250 mg/dl, did not smoke cigarettes, and had no evidence of glucose intolerance or left ventricular hypertrophy on the ECG. It is not surprising that only 8% of the men and 18% of the women in the highest weight class were free of risk factors. In the subgroup without major risk factors for disease, CVD incidence rose with increasing weight in both men and women, although the gradient of risk was clearly steeper in males than females. Moreover, logistic regression analysis in this group showed that the strength of the association between MRW and disease in both sexes was at least as great as that for men and women in the total cohort. The MRW coefficients for these males and females were 0.016 and 0.010, respectively, compared with a coefficient of 0.009 for the total population shown in table 2. Thus, the effects of obesity could be demonstrated even in those without major risk factors for disease.

The relationship of weight change to CVD incidence was examined by comparing self-reported weight at age 25 with weights at the initial Framingham examination. Although recall may be subject to some degree of bias, there is evidence from the NHLBI Twin Study\textsuperscript{25} and the Honolulu Heart Program (personal communication) that weights reported many years after age 25 years correlate fairly well with actual weights or weights reported close to that age. In this study, weight change was defined as the difference between MRW at exam 1 and MRW at age 25 years. Logistic regression analyses showed that change in MRW was positively and significantly related to risk of CVD over 26 years in both sexes even after adjustment for the effects of MRW at age 25, age at exam 1, and risk factor levels. The relative odds of developing disease corresponding to degrees of change in relative weight were calculated from the multivariate regression equation. Although women, on the average,
gained more weight than men between age 25 and entry, figure 10 shows that the net effect of weight change was greater in males than females. Nonetheless, one could conclude from these data that weight gain into the middle and older ages conveyed an increased risk of disease and weight loss a decreased risk of disease that could not be attributed either to MRW at age 25 years or the levels of the risk factors that may have resulted from weight change.

**Discussion**

These data clearly show that the degree of obesity in Framingham men and women was an important long-term predictor of CVD incidence, particularly among the younger members of the cohort. Moreover, obesity in both sexes did not exert its influence on the risk of coronary disease or congestive failure solely through its association with the coexisting risk factors. In women, significant independent relationships were evident for atherothrombotic stroke as well. The lack of association between weight and incidence of intermittent claudication, on the other hand, suggests that the cause of this disorder may be somewhat different from that of the other cardiovascular diseases. These results might also be attributed to underdiagnosis of intermittent claudication in heavier subjects who may not walk or exercise to elicit symptoms with the same frequency as leaner subjects.

It also appears that obesity predisposed to premature CVD in Framingham. Plots of the actuarial life tables for the younger members of the cohort (those younger than 50 years of age at entry to the study) show higher risks for the heaviest compared with the leanest group throughout the 26-year follow-up period (fig. 11). However, differences were more pronounced in the younger men than women.

Weight was a relatively potent risk factor for total CVD in women. Only age and blood pressure were more powerful predictors in this group. Male–female differences regarding the impact of obesity on disease

**TABLE 2. The Association Between Metropolitan Relative Weight at Entry and Cardiovascular Disease Incidence Over 26 Years in Framingham Men and Women**

<table>
<thead>
<tr>
<th>Event</th>
<th>Men (n = 2197)</th>
<th>Women (n = 2714)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.012* (636)</td>
<td>0.008* (437)</td>
</tr>
<tr>
<td>AP</td>
<td>0.014* (336)</td>
<td>0.007* (276)</td>
</tr>
<tr>
<td>CHD other than AP</td>
<td>0.009† (514)</td>
<td>0.010† (261)</td>
</tr>
<tr>
<td>MI</td>
<td>0.006 (372)</td>
<td>0.010† (161)</td>
</tr>
<tr>
<td>Death from CHD</td>
<td>0.009* (266)</td>
<td>0.010† (132)</td>
</tr>
<tr>
<td>Sudden death from CHD</td>
<td>0.016† (120)</td>
<td>0.010 (45)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.014† (177)</td>
<td>0.015† (161)</td>
</tr>
<tr>
<td>Atherothrombotic stroke</td>
<td>0.004 (105)</td>
<td>0.012† (100)</td>
</tr>
<tr>
<td>Death from CVD</td>
<td>0.006 (395)</td>
<td>0.008* (263)</td>
</tr>
<tr>
<td>Total CVD</td>
<td>0.009† (849)</td>
<td>0.009† (667)</td>
</tr>
</tbody>
</table>

Regressions include adjustments for age, systolic blood pressure, serum cholesterol, cigarettes/day, glucose intolerance, and electrocardiographic left ventricular hypertrophy at exam 1.

The number of events is given in parentheses.

*Coefficient is significantly different from zero, p < 0.05.
†Coefficient is significantly different from zero, p < 0.01.
‡Coefficient is significantly different from zero, p < 0.001.

Abbreviations: MRW = Metropolitan Relative Weight; CHD = coronary heart disease; AP = angina pectoris; MI = myocardial infarction; CVD = cardiovascular disease; n = number at risk.

**FIGURE 8. Twenty-six-year incidence of intermittent claudication by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.**

**TABLE 3. The Association Between the Major Risk Factors and Disease Incidence Over 26 Years in Framingham Men and Women**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Standardized logistic regression coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 2197)</td>
</tr>
<tr>
<td></td>
<td>CHD</td>
</tr>
<tr>
<td>Age</td>
<td>0.325</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.176</td>
</tr>
<tr>
<td>MRW</td>
<td>0.200</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.345</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>0.170</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>0.111</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>0.098</td>
</tr>
</tbody>
</table>

*Coefficients not significantly different from zero, p > 0.05.

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; MRW = Metropolitan Relative Weight; ECG-LVH = electrocardiographic left ventricular hypertrophy; n = number at risk.
infarction in Framingham men, subscapular skinfold measurements were significantly and independently associated with this outcome. Thus, it may be misleading to suggest that obesity in men did not play an important role as a precursor to infarction.

Age differences in the contribution of obesity to risk have also been noted by others.1, 4 Similarly, other risk factors for disease do not predict as well at older ages as at younger ages.4, 28 Selection has been suggested as an explanation for such findings. Here, the older, heavier subjects may have been a selective group, because they remained resistant to the influence of obesity during earlier years. However, weights at older ages may be less typical of the lifetime exposure to obesity, which may be important in determining risk. If, as suspected, age at onset and duration of obesity play a part in explaining the observed associations with disease, then earlier measurements may more accurately classify individuals into risk categories than those made in later years. The fact that certain risk factors correlated more strongly with relative weight at younger than older ages also supports the latter theory.

Population studies have shown that the extremely lean as well as the most obese are at increased risk of dying over a specified time.29 Such observations suggest that the relationships found in this study might be overstated and attributable to the phenomenon of competing risks. That is, the leaner subjects may have appeared to be at lower risk due to the fact that they died from other causes before they could develop CVD. A few simple approaches to evaluating the plausibility of such an explanation indicated that competing risks could not account for the weight-disease relationships found in Framingham men and women. The first approach entailed estimating the proportion of subjects who died of other causes but who would have been expected to develop CVD if they had lived long enough.30 The calculation of new incidence rates by level of MRW showed risks associated with increased MRW that were diminished, but only negligibly. Assuming that the leanest subjects might already be ill and die of causes other than CVD, reanalysis of the data also was undertaken including only subjects with MRW of 100 or more. The results showed associations with CVD that were at least as strong as those originally obtained.

Not only was there a powerful relationship of MRW to disease risk in Framingham, but also, the change in

\[
\begin{align*}
\text{METROPOLITAN RELATIVE WEIGHT (N)} & = \\
\text{INCIDENCE/1,000} & = \\
\text{MEN} & = \\
\text{WOMEN} & = \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & <110 \quad 10-129 \quad 130+ \\
\text{INCIDENCE/1,000} & = \\
\text{MEN} & = \\
\text{WOMEN} & = \\
\end{align*}
\]

\[
\begin{align*}
\text{RELATIVE ODDS} & = \\
\text{UNIT CHANGE IN METROPOLITAN RELATIVE WEIGHT} & = \\
\text{MEN} & = \\
\text{WOMEN} & = \\
\end{align*}
\]

**Figure 9.** Twenty-six-year incidence of cardiovascular disease by Metropolitan Relative Weight at entry among Framingham men and women younger than 50 years of age who were normotensive, had cholesterol levels less than 250 mg/dl, did not smoke cigarettes, and had no evidence of glucose intolerance or electrocardiographic left ventricular hypertrophy. \(N = \) the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.

might be explained by differences in the operation of the risk factors or in the causal pathways leading to disease. These hypotheses have been suggested by other data,26, 27 but additional factors may be responsible for the differences observed here. It is possible that the disparity in the weight distributions (that is, proportionately more women than men were extremely overweight) influenced the results to a certain degree. Relative weight also may have represented a somewhat different measure of body mass in each sex, since excess weight resulted from musculature more often in males than females. This point may be illustrated by additional analyses that describe the influence of other measures of obesity on risk. These show that while MRW was not an independent predictor of myocardial
MRW after the young adult years made an independent contribution to the prediction of CVD. At any level of MRW at age 25 years, weight change was positively and significantly associated with CVD risk in both sexes. These results illustrate not only the detrimental effects of weight gain but also the benefits of weight reduction in obesity. The stronger relationship in men than women parallels a previously reported finding of a greater influence of weight change on risk factor change in men. The present study suggests, however, that men may be more generally sensitive than women to the effects of weight change, because its impact on disease could not be attributed solely to the resulting levels of the risk factors. Although MRW at entry to the Framingham Study was a better predictor of CVD incidence than MRW at age 25 years, analyses indicate that risk was most pronounced among those who stayed in the heaviest weight class between the two time periods. These findings lend further support to the importance of duration of obesity on incidence of CVD.

The additional contribution of obesity to the long-term prediction of CVD may be its role as a precursor to the development of the major risk factors or through metabolic and physiologic mechanisms yet to be identified. It seems that the degree of obesity may, in fact, influence the later development of risk factors such as hypertension. Entry MRW in Framingham was a significant independent predictor of hypertension over 26 years in women, but not in men. Excess weight in this population may also have been associated with other lifestyle or behavioral characteristics which, over time, may have influenced CVD risk. While no data at entry were available on physical activity, diet or personality type, analyses that included an index of social class did not appear to have any impact on the relationships between weight and disease.

Other direct effects of overweight may explain its unique contribution to CVD risk. Recent data suggest that obesity is associated with fibrinolytic activity and plasma fibrinogen concentrations, which have been implicated in the onset and course of ischemic heart disease. Moreover, obesity appears to increase cardiac work load and intravascular volume and to alter glucose and lipid metabolism. Increased cardiac work load in a heavier person may precipitate an acute event or elicit symptoms if the coronary circulation is already compromised. The burden of excess weight on the heart also has been shown in autopsy studies in which relative weight was independently related to heart size. Obesity has also been associated with the extent of coronary atherosclerosis at autopsy.

Despite the findings from clinical and experimental studies, there is still much confusion over the complex relationship between obesity and CVD risk. Most epidemiologic studies have been concerned with the impact of overweight on coronary heart disease in men. These studies can be used to highlight some of the difficulties in interpreting and comparing results. For example, the Seven Countries Study showed no significant association between body mass index in most regions and coronary disease incidence over 10 years. However, many of the populations observed were considerably leaner than the Framingham cohort, whose weights compared favorably with those in the general U.S. population. The lack of sufficient heterogeneity in adiposity, and the different cultural and genetic context in which this characteristic may have operated, make comparability between these two studies difficult.

Different indexes of obesity can be differentially related to disease risk, which may explain some variability in study results. While body mass index (weight/height²) has been suggested as the preferred measure of adiposity, in Framingham it was very highly correlated with MRW (r = 0.99) and had no greater predictive power. However, skinfold measurements of subcutaneous fat accumulation correlated with MRW to a lesser degree (r = 0.40–0.65), and preliminary results suggest that these measures were associated somewhat differently with disease risk in Framingham. Furthermore, if indexes of obesity are more powerful predictors of disease in younger than older persons, differences in the age distributions of study populations may also serve to explain what appear to be conflicting results.

The length of follow-up for events in each population can also affect the conclusions drawn from various studies. Some effects of overweight may be evident only after follow-up over long periods of time, as suggested by the importance of duration of obesity on disease. Both the Framingham and Manitoba studies found obesity to be an independent predictor of disease on long-term observation only. Table 4 shows how observation over different periods of time may result in different interpretations of the same data. In Framingham men, a strong and significant association between MRW and coronary disease incidence did not emerge until the 8-year follow-up, at which point the strength of the relationship remained fairly constant for
TABLE 4. The Association Between Metropolitan Relative Weight at Entry and Coronary Heart Disease Incidence by Length of Follow-up in Framingham Men and Women

<table>
<thead>
<tr>
<th>Length of follow-up</th>
<th>Multivariate logistic regression coefficients for MRW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 2197)</td>
</tr>
<tr>
<td>6 years</td>
<td>0.006 (114)</td>
</tr>
<tr>
<td>8 years</td>
<td>0.014* (154)</td>
</tr>
<tr>
<td>14 years</td>
<td>0.012* (314)</td>
</tr>
<tr>
<td>20 years</td>
<td>0.012± (480)</td>
</tr>
<tr>
<td>26 years</td>
<td>0.012± (636)</td>
</tr>
</tbody>
</table>

Regressions include adjustments for age, systolic blood pressure, serum cholesterol, cigarettes/day, glucose intolerance, and electrocardiographic left ventricular hypertrophy at exam 1.

The number of events at different follow-up times is given in parentheses.

*Coefficient is significantly different from zero, \( p < 0.05 \).
†Coefficient is significantly different from zero, \( p < 0.01 \).
‡Coefficient is significantly different from zero, \( p < 0.001 \).

Abbreviations: MRW = Metropolitan Relative Weight; \( n \) = number at risk.

the duration of the study. Among women, the logistic coefficients were fairly strong and consistent in all observation periods. However, statistical significance was not achieved until nearly 14 years of follow-up, for the small number of events in this group resulted in insufficient power to test assumptions. Previous analyses, based on shorter periods of observation, have suggested that there is no independent relationship between MRW and coronary risk in Framingham women.14 These illustrations clearly show that the accumulated evidence describing the nature of the weight-disease relationship should be interpreted cautiously.

The issue of independence can be resolved only by further study, but we conclude from the existing data that leanness and avoidance of weight gain before middle age are advisable goals in the prevention of CVD for most American men and women. These data further indicate that intervention on the well-established risk factors for disease should be accompanied by weight loss in the overweight individual. Likewise, revisions to the actuarial desirable weight tables are premature, because such changes suggest that maintenance of heavier weights will not diminish health status. This assumption appears to be unsubstantiated by these as well as other data concerned with the impact of obesity on morbidity and mortality.1, 2, 4, 18

Acknowledgments
The authors thank Felicia Carr and Doris Scherbak for their assistance in preparing this manuscript.

References
18. Garrison RJ, Feinleib M, Castelli WP, McNamara PM: Cigarette smoking as a confounder of the relationship between relative weight and long-term mortality in the Framingham Heart Study. JAMA. In press
20. United States DH&H: Advanced Data from Vital and Health Statistics, no. 3, November 19, 1976
26. Waldron I: Sex differences in longevity. In Second Conference on
Association Between Coronary Heart Disease Risk Factors and Physical Fitness in Healthy Adult Women

LARRY W. GIBBONS, M.D., M.P.H., STEVEN N. BLAIR, P.E.D., KENNETH H. COOPER, M.D., M.P.H., AND MIKE SMITH, M.S.

SUMMARY We examined associations between physical fitness and risk factors for coronary heart disease in healthy women ages 18–65 years. Physical fitness was objectively determined by the duration of a maximal treadmill exercise test. Six physical fitness categories (very poor to superior), specific within 10-year age increments, were established. Mean risk factor levels varied across categories, but so did potential confounders such as age and weight. Multiple linear regression modeling was used to control for the effects of age, weight and year of examination on coronary risk factors. After adjustment, physical fitness was independently associated with triglycerides (p < 0.001), high-density lipoprotein cholesterol (HDL-C) (p < 0.001), total cholesterol/HDL-C ratio (p < 0.001), blood pressure (p < 0.001) and cigarette smoking (p < 0.001).

IT IS WELL ESTABLISHED that men have a higher incidence of cardiovascular disease than women. Nonetheless, coronary heart disease (CHD) is the leading cause of death in women (259 deaths/100,000 per year), with women in the United States having high rates compared with the rest of the world.1 These statistics belie the relative paucity of research in CHD epidemiology in women. Available data, notably from the Framingham study, support the classic risk factor hypothesis for CHD in women. Women with higher levels of blood cholesterol, high blood pressure, and who smoke cigarettes are more likely to develop CHD than women without these risk factors.2 Other presumed CHD risk factors have been less thoroughly studied in women. For example, several studies associating sedentary living habits with the incidence of CHD in men have been published,3-5 but we are unaware of any such studies in women. Although the precise role of physical activity in the prevention of CHD is not known, a tenable hypothesis is that more active persons have lower levels of established risk factors. We previously showed that men who were more physically fit had lower levels of CHD risk than their less physically fit peers.6 The purpose of this paper is to examine the association between physical fitness and CHD risk factors in women. We hypothesized that women with higher levels of physical fitness have a lower CHD risk.

Methods

More than 3900 adult women, ages 18–65 years, were examined from 1971 to 1980. Some women received only a treadmill test, but 2854 received a complete physical examination, including CHD risk factor measurements. Most of these women were self-referred for the purpose of physical fitness evaluation, periodic health examination or receiving preventive medical advice. These patients tended to be well educated and from middle to upper socioeconomic strata. More than 99% of the women were white. Data reported in this paper are from the first clinic visit for these...
Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study.
H B Hubert, M Feinleib, P M McNamara and W P Castelli

Circulation. 1983;67:968-977
doi: 10.1161/01.CIR.67.5.968

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/67/5/968

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/