Overweight and Obesity as Determinants of Cardiovascular Risk

The Framingham Experience

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Background: To our knowledge, no single investigation concerning the long-term effects of overweight status on the risk for hypertension, hypercholesterolemia, diabetes mellitus, and cardiovascular sequelae has been reported.

Methods: Relations between categories of body mass index (BMI), cardiovascular disease risk factors, and vascular disease end points were examined prospectively in Framingham Heart Study participants aged 35 to 75 years, who were followed up to 44 years. The primary outcome was new cardiovascular disease, which included angina pectoris, myocardial infarction, coronary heart disease, or stroke. Analyses compared overweight (BMI [calculated as weight in kilograms divided by the square of height in meters], 25.0-29.9) and obese persons (BMI ≥30) to a referent group of normal-weight persons (BMI, 18.5-24.9).

Results: The age-adjusted relative risk (RR) for new hypertension was highly associated with overweight status (men: RR, 1.46; women: RR, 1.75). New hypercholesterolemia and diabetes mellitus were less highly associated with excess adiposity. The age-adjusted RR (confidence interval [CI]) for cardiovascular disease was increased among those who were overweight (men: 1.21 [1.05-1.40]; women: 1.20 [1.03-1.41]) and the obese (men: 1.46 [1.20-1.77]; women: 1.64 [1.37-1.98]). High population attributable risks were related to excess weight (BMI ≥25) for the outcomes hypertension (26% men; 28% women), angina pectoris (26% men; 22% women), and coronary heart disease (23% men; 15% women).

Conclusions: The overweight category is associated with increased relative and population attributable risk for hypertension and cardiovascular sequelae. Interventions to reduce adiposity and avoid excess weight may have large effects on the development of risk factors and cardiovascular disease at an individual and population level.

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<18.5) is problematic. We elected to exclude them because previous experience has shown that this category was likely to include heavy cigarette consumers, those with severe chronic diseases, and persons with malignancies.8-12

Our observations spanned several decades from 1948 onward and focused on multiple measures of BMI. Unfortunately, abdominal girth, triglyceride and lipoprotein cholesterol levels, and other variables now commonly used in vascular risk assessment were not determined at these 2-year intervals. Age was taken into account in bivariate statistical models and included in all of the multivariable models, and in some instances age categories were used to investigate the development of risk factors.

###PARTICIPANTS AND METHODS

Members of the original Framingham cohort were eligible for the present study, and the original population sample included 5209 participants aged 30 to 62 years at the initial examination in 1948-1951. We used the technique of pooled repeated measures,13 an approach that allowed individuals to contribute multiple person examinations to the analysis as long as they met the inclusion criteria at the beginning of each observation interval. Specifically, persons free of CVD at an examination and with a BMI of 18.5 or greater were eligible for the next period of observation.4-12 Weight, blood pressure, serum cholesterol, cigarette smoking in the previous year, menopausal status in women, and interim medication use were ascertained for each participant at each biennial clinic examination.

Weight was determined to the nearest pound on a physician’s scale. Stature, measured to the nearest quarter inch at the initial Framingham Heart Study examination, was used. Height and weight were converted to meters and kilograms, allowing the calculation of BMI for participants at each examination. The BMI categories (overweight: BMI, 25.0-29.9; obese: BMI ≥30; normal: BMI, 18.5-24.9) were used in the statistical analyses.8 Individuals with an arterial pressure of 140/90 mm Hg or higher or taking hypertensive medication were classified as hypertensive. Persons with a casual blood glucose level of 200 mg/dL (11.1 mmol/L) or greater at the clinic examination, receiving oral hypoglycemic therapy, or taking insulin were categorized as having diabetes mellitus, using American Diabetes Association 1997 criteria.14 For the present investigation, hypercholesterolemia was defined as a clinic blood cholesterol level of 240 mg/dL (6.2 mmol/L) or greater or reported use of lipid-lowering therapy since the last clinic examination.15,16 Women who reported no menstrual periods during the 12 months prior to a clinic examination were considered menopausal from that time forward. Data from subsequent examinations were used to reclassify subjects according to their current age, BMI, diabetes mellitus status, serum cholesterol level, cigarette smoking, and hypertension status.

Participants were monitored over 2 years after each examination for the occurrence of an initial CVD event, and participants were followed up to 44 years for changes in risk factor status. The coronary heart disease (CHD) end points considered were angina pectoris, myocardial infarction, and coronary death. Myocardial infarction and coronary death were grouped together as “hard CHD,” and the initial occurrence of any of the 3 CHD end points was labeled “total CHD.” Cerebrovascular disease included the occurrence of new strokes and transient ischemic attacks, and the end point total CVD was used for persons who developed either CHD or cerebrovascular disease. The end points for cardiovascular and cerebrovascular disease were adjudicated by senior Framingham Study scientists during follow-up, and the diagnostic criteria for the clinical events have been published elsewhere.17

Age-specific incidence rates for the first occurrence of hypertension, hypercholesterolemia, diabetes, myocardial infarction, angina pectoris, cerebrovascular disease, total CHD, and total CVD were calculated according to the most recently determined BMI category. Analyses were age-adjusted and multivariable adjusted, including the variables age, hypertension, hypercholesterolemia, and cigarette smoking. Adjustment for menopausal status was also included for women in multivariable analyses.

The β coefficients in the pooled logistic regression analyses were exponentiated to estimate the RR. The SE of the β coefficients was used to calculate the 95% confidence intervals (CIs) of the RR estimates using published methods.18 Population attributable risk (PAR) was calculated from the category-specific RR estimate and the prevalence of the factor using the following equation:

\[
\text{PAR} = \frac{\text{Proportion of Cases Exposed to the Factor}}{\times 100 \times (\text{RR} - 1)/\text{RR}}
\]

When the RR estimate was less than 1.0, the PAR estimate was negative, representing a potentially preventive effect.19-21 The PAR values for the overweight and obese categories were added together to estimate the effects of a composite overweight category on risk factor development and the occurrence of CVD.

###RESULTS

Characteristics of the participants are given in Table 1 for men and women according to categories of BMI. The person-years of experience (bottom row of Table 1) reflect the cross-sectional pooling of the data over the 44 years of follow-up. The age entries within the columns give the percentage distribution of the follow-up experience within a given BMI category. For instance, men aged 56 to 65 years comprised 29% of data experience for the 18.5 to 24.9 BMI category. The prevalences of risk factors at entry into the study are shown to generally increase with age. The proportions with elevated cholesterol levels (>240 mg/dL [6.2 mmol/L]) and cigarette use reflect the higher mean cholesterol levels and a greater proportion of the population smoking in the late 1940s and early 1950s.

The development of new risk factors and incidence of new events are given in Table 2 for men and women according to BMI category. The highest incidence rates
consistently observed were for the development of hypertension, hypercholesterolemia, and the aggregate development of any of the risk factors (top row of Table 2). The RRs for the new development of risk factors according to BMI category appear in Table 3. Age- and multivariable-adjusted estimates are provided, accompanied by the 95% CI and the 95% CI for this estimate was 1.75 to 2.84. The proportion of new hypertension attributable to the obesity category was 8% in men. As the BMI categories were mutually exclusive, the PAR estimates could be added together, and the overall effect of overweight or obesity categories on new hypertension (composite PAR) was 26% (18%+8%) in men and 28% (17%+11%) in women. Similarly, the RRs and PAR estimates for the occurrence of hypercholesterolemia (composite PAR, 10% in men and 9% in women) and diabetes mellitus (composite PAR, 21% in men and 3% in women) are given in Table 3.

The RRs for new vascular disease events and mortality are presented in Table 4 and Table 5 for men and women, respectively. These tables duplicate the format of Table 3. Excess adiposity was generally associated with a significantly increased RR for cardiovascular events in men, but no greater risks for myocardial infarction or CVD death were observed. Relative risks for vascular events associated with overweight and obesity were often lower in women. The composite PAR estimates for a BMI of 25 or greater and total CVD (obtained by adding the PAR estimates for overweight and obesity) were 15% in men and 10% in women. Similarly, the composite PAR estimates for a BMI of 25 or greater and angina pectoris were 26% in men and 22% in women.

The PAR percentage estimates from Tables 3 through 5 are shown in the Figure for men and women. This display generally shows that the PAR levels for the risk factors and CVD end points are generally similar in women and men, except for hypertension, which was much greater in women. In addition, the relative contribution of the overweight category to the occurrence of risk factor development typically equals the contribution made by the obesity category. This tendency holds for risk factors and CVD events in both sexes, with a few exceptions, except for the more serious events among women, in whom the effect of obesity was much greater than the effect of overweight. In a few instances, the PAR estimates were negative for overweight (BMI, 25.0-29.9) women, indicative of a protective effect. With the exception of CVD death in women, these effects were generally mild and not statistically significant, and the pertinent RR estimates are given in Table 5.

This investigation concerning overweight, obesity, and its cardiovascular sequelae differs from previous reports in that it focuses on the incidence of vascular risk factors and CVD sequelae according to specified categories of adiposity that have been promulgated by American and international expert panels. Our analysis eliminated several features that may have affected reporting in the past. We adjusted for cigarette smoking, hypertension, and diabetes mellitus and excluded persons with subnormal levels of BMI. Cross-sectional pooling methods were used, affecting interpretation of the findings. This analytic technique reassessed the population every 2 years, and the findings reflect the effects of adiposity evaluated close to the time that new risk factors or vascular disease outcomes developed.

Both the overweight and obesity categories were highly related to the risk of hypertension in men and women. The RR ranged from 1.5 to 1.7 for overweight and 2.2 to 2.6 for obese persons. The corresponding composite PAR estimates were greatly increased, and a BMI of 25 or greater accounted for approximately 34% of hypertension in men and 62% in women. Other factors, especially excessive alcohol consumption and estrogen use in women, have been shown to increase the risk of hypertension, but the population impact is smaller because the prevalence of each of those factors is lower. Greater intake of sodium and lower consumption of potassium and calcium have also been linked to the occurrence of hypertension, but we did not have serial dietary information to investigate the role of these cations.

Previous research in the second-generation Framingham Heart Study Offspring cohort has shown that a variety of factors, including relative weight, heart rate, alcohol intake, and levels of hematocrit, blood glucose, serum protein, triglyceride, and phosphorus, were related to hypertension occurrence in one or both sexes. Excess adiposity has loomed as the most controllable antecedent factor. Clustering of traditional cardiovascular risk factors has been reported in obese or hypertensive individuals, and the average number of metabolic abnormalities has been shown to rise monotonically in proportion to the degree of adiposity.

Different relations were obtained between adiposity and new hypercholesterolemia. First, cholesterol levels of 240 mg/dL (6.2 mmol/L) or higher were more common at the outset of the study, and levels have declined over the past few decades. Second, total cholesterol levels tend to increase between ages 20 and 60 years, and

### Table 2. Incidence of Risk Factors and Events<sup>*</sup>

<table>
<thead>
<tr>
<th>Risk Factor or Event</th>
<th>BMI Category, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4/0.4</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10.2/13.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.1/1.3</td>
</tr>
<tr>
<td>Any one of above</td>
<td>14.7/16.5</td>
</tr>
<tr>
<td>Event</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1.1/0.7</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.3/0.4</td>
</tr>
<tr>
<td>Hard CHD</td>
<td>1.4/0.4</td>
</tr>
<tr>
<td>Total CHD</td>
<td>2.3/1.1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.5/0.4</td>
</tr>
<tr>
<td>Total CVD</td>
<td>3.8/2.1</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.7/0.4</td>
</tr>
<tr>
<td>Total mortality</td>
<td>2.4/1.2</td>
</tr>
</tbody>
</table>

<sup>*</sup>Data are incidence (per 1000 person-years) of participants (men/women). BMI indicates body mass index; CHD, coronary heart disease; and CVD, cardiovascular disease.
the low-density and very low-density lipoprotein cholesterol fractions rise, while the high-density lipoprotein cholesterol fractions remain stable or decline slightly.\(^32\) Unfortunately, serial measurements for the lipoprotein fractions were not available over the course of this investigation. During follow-up, the overweight participants (but not those who were obese) experienced an increased risk for new hypercholesterolemia (Table 3). The nonsignificant result in the obese individuals may be partly attributable to a greater prevalence of elevated cholesterol level in the obese group at baseline. In contrast to the findings for hypertension, only 10% of elevated cholesterol in men and 9% of elevated cholesterol in women was attributable to overweight and obesity (Table 3). Previously published cross-sectional studies have shown that greater levels of BMI are generally associated with greater cholesterol and triglyceride levels, reduced high-density lipoprotein cholesterol, and smaller low-density lipoprotein particles.\(^33,34\)

The incidence of new diabetes mellitus was increased in overweight men and obese persons of both sexes. No tendency toward an increased risk for diabetes mellitus was observed for “overweight” women, suggesting that hormonal factors may play a role. By our analysis, approximately 21% of diabetes in men was attributable to overweight and obesity, and in women only 3% of diabetes was attributable to excess adiposity. The findings are highly plausible in men, but there is no ready explanation for the weaker relations in women. A variety of issues should be considered. First, it is possible that BMI does not adequately characterize corpulence and that regional adiposity measures such as abdominal girth would have classified women better and improved the prediction.\(^35\) Second, the prediabetic state is often catabolic, and weight loss may have occurred prior to the diagnosis of type 2 diabetes mellitus. That explanation still would not account for the sex difference in RRs. Third, age, lipoprotein cholesterol fractions, inflammatory markers, and hepatic adiposity measures such as abdominal girth would have classified women better and improved the prediction.\(^35,36\)
 Cardiovascular outcomes were highly associated with adiposity, as shown in Tables 4 and 5 for men and women, respectively. Framingham obesity and CVD results have been presented in different forms over the years, including units of relative weight and percentiles of obesity, but not with the design to gauge the impact with attributable risk estimates and modern categories of adiposity. Our data showed that total CHD in men was highly associated with overweight and obesity, and the RR was stronger for the obesity category. Of note, however, is that the PAR estimate for total CHD was greater for the overweight category than for the obese category. This result cannot easily be attributed to a greater prevalence of overweight in men than in women (Table 1). Perhaps gonadal hormones, other male and female differences, or factors not available for this analysis were responsible for this effect. On the other hand, overweight and obesity appeared to exert similar effects on total CHD risk in women. The RR for total CHD was of borderline significance in overweight women, but was highly significant in obese women. The results for total CVD generally paralleled what was observed for CHD in both sexes across the overweight and obese categories. In this instance, however, all associations were statistically significant, and the composite PAR estimates for total CVD were 16% for men and 17% for women.

The adiposity categories tended to have different effects on the various cardiovascular outcomes in men and women (Tables 4 and 5). The end points most highly associated with overweight and obesity among men were angina pectoris (composite PAR, 26%) and total CHD (composite PAR, 23%). Negligible effects were observed for CVD death. Similarly, among women, angina pectoris (composite PAR, 22%) and total CHD (composite PAR, 15%) were highly associated with overweight and obesity. As the analytic method undertook reappraisal of events and risk factors at 2-year intervals, only participants free of CVD were included in subsequent follow-up intervals. Outcomes that were not first cardiovascular events, such as cerebrovascular disease and cardiac death that typically occur in older persons, would not be expected to be highly associated with adiposity under these circumstances.

Table 5. Relative Risk and Population Attributable Risk Percentage for Adiposity Categories and Vascular Disease Outcomes for Women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BMI 25-29.9 kg/m²</th>
<th>BMI ≥ 30 kg/m²</th>
<th>Composite (BMI ≥ 25 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted RR (95% CI)</td>
<td>Multivariable-Adjusted RR (95% CI)</td>
<td>Population Attributable Risk, %</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1.58 (1.21-2.05)</td>
<td>1.42 (1.08-1.86)</td>
<td>13</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.96 (0.65-1.42)</td>
<td>0.91 (0.61-1.36)</td>
<td>-3</td>
</tr>
<tr>
<td>Hard CHD</td>
<td>1.03 (0.72-1.46)</td>
<td>0.98 (0.69-1.41)</td>
<td>-1</td>
</tr>
<tr>
<td>Total CHD</td>
<td>1.32 (1.07-1.62)</td>
<td>1.22 (0.99-1.52)</td>
<td>7</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.18 (0.83-1.66)</td>
<td>1.10 (0.77-1.56)</td>
<td>4</td>
</tr>
<tr>
<td>Total CVD</td>
<td>1.20 (1.03-1.41)</td>
<td>1.13 (0.96-1.33)</td>
<td>4</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.77 (0.50-1.17)</td>
<td>0.77 (0.50-1.18)</td>
<td>-9</td>
</tr>
</tbody>
</table>

*Referent group is normal weight (body mass index [BMI], 18.5-24.9 kg/m²). RR indicates relative risk; CI, confidence interval; CHD, coronary heart disease; and CVD, cardiovascular disease.
†Multivariable adjusted for age, smoking, hypertension, hypercholesterolemia, and diabetes.
The findings we reported differ from those reported by others who have asserted that “overweight is not consistently associated with coronary heart disease risk.” Our data merit attention, as they tend to contravene the preceding statement. In the Framingham experience, overweight and obesity were highly related to incident hypertension, diabetes mellitus, and angina pectoris. Among overweight persons, RR's were slightly stronger in men, but among the obese the RR's were often greater in women. Past age 50 years, overweight and obesity were very common in women, and this tendency toward greater adiposity, combined with moderately increased RR's that accompany the condition, led to impressive PAR estimates for the development of CVD risk factors and events (Tables 3-5; Figure 1).

It is reasonable to generalize from our results to other population groups. We excluded underweight participants in an effort to provide a healthy comparison group of normal weight, but the Framingham population sample is largely a middle-class, middle-aged white cohort. Different results might be obtained in population samples with a different ethnic identity and in the present era when hypertension, diabetes mellitus, and hypercholesterolemia may be more effectively identified and treated. On the other hand, our data may more accurately reflect the influence of adiposity on risk factors and CVD not modified by treatment.

In summary, overweight and obesity were associated with an increased RR for the development of cardiovascular risk factors and CVD itself. The effects were consistently seen across cardiovascular end points and significant adverse sequelae were typically observed even in persons who were overweight but not obese, highlighting the importance for primary prevention and treatment of moderate degrees of excess adiposity.

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