Weight, Weight Change, and Coronary Heart Disease in Women
Risk Within the ‘Normal’ Weight Range

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Objective.—To assess the validity of the 1990 US weight guidelines for women that support a substantial gain in weight at approximately 35 years of age and recommend a range of body mass index (BMI) (defined as weight in kilograms divided by the square of height in meters) from 21 to 27 kg/m², in terms of coronary heart disease (CHD) risk in women.

Design.—Prospective cohort study.

Setting.—Female registered nurses in the United States.

Participants.—A total of 115,618 women aged 30 to 55 years in 1976 and without a history of previous CHD.

Main Outcome Measure.—Incidence of CHD defined as nonfatal myocardial infarction or fatal CHD.

Results.—During 14 years of follow-up, 1292 cases of CHD were ascertained. After controlling for age, smoking, menopausal status, postmenopausal hormone use, and parental history of CHD and using as a reference women with a BMI of less than 21 kg/m², relative risks (RRs) and 95% confidence intervals (CIs) for CHD were 1.19 (0.97 to 1.44) for a BMI of 21 to 22.9 kg/m², 1.46 (1.20 to 1.77) for a BMI of 23 to 24.9 kg/m², 2.06 (1.72 to 2.48) for a BMI of 25 to 28.9 kg/m², and 3.56 (2.96 to 4.29) for a BMI of 29 kg/m² or more. Women who gained weight from 18 years of age were compared with those with stable weight (±5 kg) in analyses that controlled for the same variables as well as BMI at 18 years of age. The RRs and CIs were 1.25 (1.01 to 1.55) for a 5- to 7.9-kg gain, 1.64 (1.33 to 2.04) for an 8- to 10.9-kg gain, 1.92 (1.61 to 2.29) for an 11- to 19-kg gain, and 2.65 (2.17 to 3.22) for a gain of 20 kg or more. Among women within the BMI range of 18 to 25 kg/m², weight gain after 18 years of age remained a strong predictor of CHD risk.

Conclusions.—Higher levels of body weight within the “normal” range, as well as modest weight gains after 18 years of age, appear to increase risks of CHD in middle-aged women. These data provide evidence that current US weight guidelines may be falsely reassuring to the large proportion of women older than 35 years who are within the current guidelines but have potentially avoidable risks of CHD.

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MOST researchers would agree that extreme degrees of obesity increase the risk of coronary heart disease (CHD) in both men and women; however, the importance of more modest degrees of overweight is controversial. Furthermore, while weight gain through the adult years is usual, the health consequences of this weight gain are a focus of debate. These questions have direct implications for establishing weight recommendations, which provide guidance for individuals and their health care providers. In the 1990 US weight guidelines, the range of desirable weights for men and women aged 35 years and older was increased to correspond with body mass indexes (BMIs) (defined as weight in kilograms divided by the square of height in meters) of 21 to 27 kg/m², in contrast to approximately 19 to 24 kg/m² in the 1985 US guidelines. This change greatly increased the upper limit of desirable weight, and the higher weights for persons older than 35 years also implied that weight gains of 4.5 to 6.8 kg were consistent with good health. Furthermore, the guidelines suggest that a BMI less than 21 kg/m² is unhealthy. The 1990 guidelines also indicated that the presence of obesity-related complications, such as diabetes or hypertension, should be used to evaluate the seriousness of a person’s overweight. With either set of guidelines, individuals who initially were lean could increase their weight markedly during adulthood and still remain within the “desirable” range; the new guidelines would include as reasonable gains of up to 18 kg. A change-in-weight criterion has not been part of weight guidelines, but may be a potentially useful predictor of disease risk. Because increases in weight largely reflect fat mass, these increases may predict risk within ranges of attained weights that are plausibly due to differences in muscle or bone mass. Furthermore, changes in weight are simpler to communicate than are weight-for-height indexes.

We previously reported a strong positive association between obesity and risk of CHD during 8 years of follow-up among women in the Nurses’ Health

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Study. We have now examined this relationship after 14 years to obtain more precise information about the dose–response relationships for both attained weight and change in weight as an adult. In these analyses we specifically did not control for history of hypertension, diabetes, or hypercholesterolemia because these factors are intermediate in the causal pathway between adiposity and CHD. Controlling for these risk factors can provide insight into mechanisms by which adiposity causes CHD, but doing so removes statistically the real metabolic consequences of excess weight and would provide a misleading description of the effects of excess body weight on risk of CHD.\(^6\) We also determined the risks related to being overweight among women without diabetes and hypertension to determine whether risk was increased in the absence of diagnosis of these conditions.

**METHODS**

The Nurses’ Health Study was established in 1976 when 121,700 female registered nurses aged 30 to 55 years returned a postal questionnaire about their medical histories and lifestyles. Further details have been published elsewhere.\(^{11,22}\) The women in this analysis were the 115,618 who were free of diagnosed CHD in 1976 and not pregnant at that time.

**Risk Factor Data**

On the 1976 questionnaire we requested information about age, current weight and height, current and past smoking, parental history of myocardial infarction, reproductive history, use of oral contraceptives or postmenopausal hormones, and personal history of myocardial infarction or angina pectoris as well as other diseases. Follow-up questionnaires have been sent at 2-year intervals to update this information and ascertain the occurrence of major illnesses. In 1980 the participants were asked to record their weight at the age of 18 years. This information was obtained from 80% of the participants, who did not differ appreciably from the remaining cohort members with regard to BMI in 1976 or other CHD risk factors (data available from authors on request).

**Documentation of CHD**

The primary end point for this analysis was CHD, which included symptomatic nonfatal myocardial infarction or fatal CHD that occurred after the return of the 1976 questionnaire but before June 1, 1990. The follow-up rate for nonfatal events through 1990 was 96% of the total potential 1,560,478 person-years of follow-up. Nonfatal infarctions were corroborated by hospital records (79%) or by letter or telephone interviews (21%) as described previously.\(^5\) Fatal CHD was ascertained using the National Death Index and confirmed by hospital records or autopsy.\(^5,23\)

**Calculation and Validation of Anthropometric Variables**

The primary measure of adiposity in this analysis was BMI. This commonly used index is minimally correlated with height (\(r=-.08\) in this population) and highly correlated with height-adjusted fat mass measured by underwater weighing in young and middle-aged women (\(r=.8\) to .9).\(^3\) For comparison with other studies, we categorized women into groups of BMI corresponding to less than 21 kg/m\(^2\), 21 to 22.9 kg/m\(^2\), 23 to 24.9 kg/m\(^2\), 25 to 28.9 kg/m\(^2\), and 29 kg/m\(^2\) or more. We also used height reported on the 1976 questionnaire and weight at 18 years of age reported in 1980 to calculate BMI at 18 years of age. We also calculated weight change from 18 years of age to 1976.

In a subset of 184 participants described elsewhere,\(^19\) the correlation between self-reported and directly measured weight was .96. Among a sample of participants in the companion Nurses’ Health Study II (data available from authors on request), self-reported weight at 18 years of age was strongly correlated with recorded weights at entry to college or nursing school (\(r=.87\)). Current height reported at the time of entry into the study was also strongly correlated with height noted in the same records (\(r=.94\)). Although women tended to overreport height slightly and to underreport weight, the bias in the BMI at 18 years of age was small (0.6 BMI units).

**Statistical Analysis**

Women were classified according to their BMI in 1976, BMI at 18 years of age (in quintiles), and change in weight from 18 years of age to 1976. Person-years of exposure were calculated from the date of return of the 1976 questionnaire to the date of nonfatal myocardial infarction or fatal CHD or June 1, 1990, whichever came first. For women who developed a nonfatal myocardial infarction and died of fatal CHD during a subsequent 2-year follow-up interval, we only included follow-up time to the nonfatal event to avoid double-counting CHD.

Relative risks (RRs) were adjusted for 5-year categories of age using stratified analyses. Because the leanest group included more women who smoked cigarettes,\(^3\) which substantially increases risk of CHD, we also controlled for smoking and other risk factors simultaneously using proportional hazards models. The absolute excess risks (attributable risks) due to adiposity (using the incidence rate for women with a BMI of <21 kg/m\(^2\) as the reference) or weight change (using those with a <5-kg weight change as the reference) were calculated using the multivariate RRs as described by Wacholder et al.\(^11\)

**RESULTS**

**BMI at Baseline**

During the 14 years of follow-up (1,560,478 person-years), we documented 12,922 incident cases of CHD, including 991 nonfatal infarctions and 889 fatal events. In the age-adjusted analysis, risk of CHD increased more with increasing BMI in 1976 (Table 1). Comparing women with a BMI of 29 kg/m\(^2\) or more with those whose BMI was less than 21 kg/m\(^2\), the RR was 2.90 (95% confidence interval [CI], 2.43 to 3.46). The RRs were similar for nonfatal myocardial infarction (RR=3.15; 95% CI, 2.56 to 3.87) and fatal CHD (RR=2.73; 95% CI, 2.01 to 3.72), so these end points were combined in subsequent analyses. The RRs of CHD associated with higher levels of BMI were appreciably greater in multivariate analyses (Table 1), primarily because these analyses accounted for the excess number of current smokers among lean women. For women with a BMI of 29 kg/m\(^2\) or more, the RR was 3.56 (95% CI, 2.96 to 4.29). Even women with BMIs below average and not considered overweight were at excess risk of CHD; for example, the risk was nearly 50% greater among women with a BMI between 23 and 24.9 kg/m\(^2\) compared with the leanest women.

In separate age-specific analyses, RRs for women with a BMI of 29 kg/m\(^2\) or more were 4.25 (95% CI, 2.18 to 8.29) for those younger than 45 years in 1976, 3.15 (95% CI, 1.15 to 9.18) for those aged 45 to 49 years, and 4.09 (95% CI, 3.31 to 5.06) for those aged 50 years. When we repeated the overall analyses updating the BMI at the beginning of each 2-year follow-up interval, similar relationships with CHD risk were seen (data available from authors on request). We also further subdivided women in the lowest category into those with BMIs of less than 18.5 kg/m\(^2\) and 18 to 20.9 kg/m\(^2\), but found little additional gradient in risk (RR=0.94; 95% CI, 0.70 to 1.25) for BMIs of 18 to 20.9 kg/m\(^2\) using a BMI of less than 18 kg/m\(^2\) as the referent.

**BMI at 18 Years of Age**

Most women had been much leaner at 18 years of age. Whereas nearly half had BMIs more than 23.3 kg/m\(^2\) in 1976, only approximately one fifth had this degree of adiposity at 18 years of age. When
only weight at 18 years of age was examined, only the women in the highest BMI quintile were at significantly increased risk of CHD (RR=1.53; 95% CI, 1.64 to 2.40) (Table 1). When both the BMI at 18 years of age and in 1976 were included in the same model, the association with the BMI in 1976 remained essentially unchanged, whereas virtually no relationship remained with the BMI at 18 years of age. Thus, attained adult weight appeared to be the important variable, and a high BMI at 18 years of age likely was associated with increased risk because of its contribution to the BMI in 1976.

Weight Gain

Weight gain from 18 years of age to 1976 was strongly associated with risk of CHD during the next 14 years when adjusted for the BMI at 18 years of age and other coronary risk factors (Table 2). Compared with women with a weight change of less than 5 kg, the RR for those who gained 20 kg or more was 2.65 (95% CI, 2.17 to 3.22). Even those gaining 5 to 7.9 kg experienced a significant excess risk of CHD (RR=1.26; 95% CI, 1.01 to 1.55). When change in weight was considered as a continuous variable, risk of CHD increased by 3.1% (95% CI, 2.6% to 3.6%) for each kilogram of weight gain. The number of women who lost substantial weight after 18 years of age was few; RRs of CHD for these women were near 1.0, but the CIs were wide. In age-specific analyses of weight change, the RRs were slightly higher for the youngest women but did not indicate any clear pattern with age. Compared with women with less than 5 kg of weight change, the RRs for those gaining 20 kg or more were 4.30 (95% CI, 1.88 to 9.82) for those younger than 45 years in 1976, 1.44 (95% CI, 0.75 to 2.77) for those aged 45 to 49 years, and 2.84 (95% CI, 2.29 to 3.52) for those aged 50 years or older.

Among women who in 1976 had a BMI between 18 and 25 kg/m², which has been suggested as a possible range for desirable weights, previous weight change was still highly predictive of future CHD risk. Compared with women whose weights changed by less than 5 kg from 18 years of age, RRs were 1.27 (95% CI, 0.99 to 1.64) for a gain of 5 to 7.9 kg, 1.56 (95% CI, 1.17 to 2.06) for a gain of 8 to 10.9 kg, 1.74 (95% CI, 1.29 to 2.35) for a gain of 11 to 19 kg, and 2.62 (95% CI, 1.12 to 6.11) for a gain of 20 kg or more.

We also examined the association between weight change and risk of CHD separately according to BMI at 18 years of age (Figure). Within each category of weight at 18 years of age, a clear gradient of greater risk was seen with increasing weight gain. Compared with women who were lean at 18 years of age and gained or lost less than 5 kg, virtually all others were at increased risk of CHD.

Risks Among Women Without History of Hypertension or Diabetes and by Smoking Status

Since the current weight guidelines imply that high body weights may be relatively benign in the absence of weight-related complications, we examined the association between BMI in 1976 and subsequent risk of CHD among women without diabetes or hypertension at baseline. Multivariate RRs were similar to those among all women; for categories of BMI as in Table 1, RRs were 1.0, 1.25 (95% CI, 1.00 to 1.57), 1.53 (95% CI, 1.21 to 1.93), 2.04 (95% CI, 1.62 to 2.56), and 2.57 (95% CI, 1.99 to 3.38). These RRs did not change appreciably in an additional analysis censoring follow-up after any diagnosis of diabetes, hypertension, or high blood cholesterol between 1976 and 1990, even though the number of incident cases of CHD was reduced from 781 to 440 (for the same categories of BMI, the RRs were 1.0, 1.25 [95% CI, 0.94 to 1.66], 1.69 [95% CI, 1.20 to 2.15], 1.84 [95% CI, 1.37 to 2.48], and 2.25 [95% CI, 1.57 to 3.24]). The self-reported diagnoses of diabetes, hypertension, or high blood cholesterol may not, of course, have included all early cases of these conditions.

We also examined the association between BMI and CHD risk among women who currently smoked cigarettes as well as those who did not. Strong linear relationships were seen among both groups; for those with a BMI of 29 kg/m² or greater, the multivariate RRs were 3.26 (95% CI, 2.58 to 4.12) among current smokers and 4.36 (95% CI, 3.12 to 6.09) among never or past smokers when compared with women with a BMI of less than 21 kg/m².

Absolute Excess Risk

Of the overall incidence of CHD in this cohort, 37% was accounted for by excessive body weight, defined as a BMI of 21 kg/m² or greater. For women with a BMI of 29 kg/m² or greater, 72% of their risk could be accounted for by their excess weight. Viewed alternatively, 27% of the overall incidence could be accounted for by weight gains of 5 kg or more after 18 years of age, and 62% of the risk among those gaining 20 kg or more could be attributed to weight gain. Among women not currently smoking, 46% of their incidence of CHD could be attributed to excess attained body weight and 30% to their weight gain after 18 years of age.

COMMENT

In this prospective cohort study of women, higher levels of adiposity as...
Table 2.—Relative Risk (RR) and 95% Confidence Interval (CI) of Coronary Heart Disease by Weight Change From 18 Years of Age to 1976*

<table>
<thead>
<tr>
<th>Weight Change, kg</th>
<th>Person-Years</th>
<th>No. of Cases</th>
<th>Multivariate RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss ≥ 20</td>
<td>6114</td>
<td>8</td>
<td>1.09</td>
<td>0.53-2.21</td>
</tr>
<tr>
<td>Loss 11-19.9</td>
<td>23,626</td>
<td>28</td>
<td>1.15</td>
<td>0.77-1.71</td>
</tr>
<tr>
<td>Loss 5-10.9</td>
<td>76,796</td>
<td>49</td>
<td>0.78</td>
<td>0.57-1.06</td>
</tr>
<tr>
<td>Loss 4.9-Gain 4.9</td>
<td>474,815</td>
<td>253</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Gain 5-7.9</td>
<td>199,135</td>
<td>128</td>
<td>1.25</td>
<td>1.01-1.55</td>
</tr>
<tr>
<td>Gain 8-10.9</td>
<td>140,471</td>
<td>127</td>
<td>1.65</td>
<td>1.33-2.05</td>
</tr>
<tr>
<td>Gain 11-19</td>
<td>229,427</td>
<td>260</td>
<td>1.92</td>
<td>1.61-2.29</td>
</tr>
<tr>
<td>Gain ≥ 20</td>
<td>111,686</td>
<td>176</td>
<td>2.65</td>
<td>2.17-3.22</td>
</tr>
</tbody>
</table>

*Adjusted for age (5-year categories), smoking status (past, never, or current smoking of 1 to 14, 15 to 24, or 25 or more cigarettes per day), menopausal status, current and past use of postmenopausal hormones, parental history of myocardial infarction before 60 years of age, BMI at 18 years of age (categories as in Table 1), and 5-year follow-up intervals.

Ellipses indicate reference category.

Relative risk of coronary heart disease by level of body mass index (BMI) (defined as weight in kilograms divided by the square of height in meters) at 18 years of age and weight gain between 18 years of age and 1976. Plus signs indicate weight gain; minus signs, weight loss. Women with a BMI of less than 19.1 kg/m² at 18 years of age and with stable weight were the reference category. The darker shaded categories include the current range of recommended BMI values for adults older than 35 years.¶ Women with a BMI less than 21.6 kg/m² at 18 years of age who lost 5 kg or more body weight were too few to compute relative risks.

assessed by the BMI were monotonically related to increasing incidence of nonfatal myocardial infarction and fatal CHD. Even women somewhat below the average BMI had a significantly increased risk of CHD compared with the leanest women. Furthermore, even a modest degree of weight gain subsequent to 18 years of age was associated with higher risk of CHD. The lowest risks were among those women who were lean at 18 years of age and did not gain or lose appreciable weight after that time.

The large number of end points during 14 years of follow-up in this cohort allows a more precise quantification of the dose-response relationship than has been possible previously. The overall magnitude of association was also similar to that observed in our previous report based on fewer than one third the number of myocardial infarctions, among women in the American Cancer Society cohort and in the Framingham study. Because substantial decreases in lean body mass, often accelerated by disease or inactivity, occur frequently in the elderly, BMI and changes in weight are likely to be much poorer indicators of adiposity among older persons. Thus, our findings apply directly to younger and middle-aged women, among whom most of the gains in weight during adult life occur. Our findings are also consistent with a recent cross-sectional analysis among middle-aged men and women in the Framingham population. In that analysis, almost all persons of both genders with a BMI of 25 kg/m² or more, as well as almost half of persons with a BMI of 23 to 25 kg/m², experienced adverse effects on blood pressure, glucose control, or lipid metabolism. Therefore, both metabolic and epidemiologic studies indicate adverse consequences even at levels of BMI not generally considered to represent overweight.

Data on weight gain and risk of CHD in women have been limited. In our earlier analysis based on far fewer cases of CHD, a significant increase in risk was not observed with less than 10 kg of weight gain, whereas a clear excess is now seen with even 5 to 7.9 kg of gain. In a recent report by Must et al, relative weight at 18 years of age predicted future risk of CHD death among men but not women. Because of the relatively small size of that cohort (19 CHD deaths among 252 women), however, the CI included the increased risk that we observed among women with a BMI of 23.3 kg/m² or greater at 18 years of age.

In our data the increased risk among the heaviest women at 18 years of age was no longer evident after accounting for the BMI in 1976, indicating that the influence of adolescent weight is mediated by its correlation with weight in midlife. Although more immediate rather than remote weight is apparently the underlying risk factor for CHD in women, overweight in adolescence is predictive of midlife weight. Also, the cumulative lifetime risk of CHD will be greatest among those who are overweight throughout their years at risk. Although weight at 18 years of age did contribute to increased risk of CHD, increases in weight after that age accounted for most of the excess.

We did not explicitly control for specific dietary factors, which were not assessed until 1980. However, intake of specific nutrients were minimally associated with BMI in this cohort; hence, these nutrients could not have appreciably influenced the associations we observed. We chose not to control for physical activity, which has been associated with both lower risk of CHD as well as leanness, because physical activity is a critical component of long-term weight control. Also, we did not have data on body circumferences at the onset of this study, so the independent contribution of body fat distribution will need to be assessed during future analyses.

The 1990 US weight guidelines that are based on a BMI range of approximately 21 to 27 kg/m² for men and women older than 35 years would identify only 17% of the cohort as being at increased risk of CHD due to excessive weight. The guidelines thus provide false reassurance to the large fraction of the population who are not defined as overweight, but who are at substantially increased risk of CHD (31% with a BMI of 23 to 27 kg/m²). The strong gradient in risk associated with weight change in an analysis restricted to women with a BMI between 18 and 25 kg/m² supports the

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use of a lower range of both attained weight and weight change in setting guidelines. We found that the lowest risk of CHD occurred among women with a BMI of less than 21 kg/m², which is below the current range of desirable weights. This clear gradient in risk we found among women without hypertension or diabetes is likely related in part to the high future risk of these conditions among overweight women.20,21 Hence, overweight cannot be ignored even if complications are not yet apparent.

Considerations regarding weight guidelines should, of course, take into account other causes of morbidity and mortality in addition to CHD. We chose to focus on fatal CHD and nonfatal myocardial infarctions rather than total mortality in these analyses, since CHD represents a large proportion of major illnesses in US women and such analyses provide the best understanding of biological relationships between adiposity and this disease. Although the strong association between BMI and fatal CHD disease is diluted by other causes of death unrelated to BMI, we did not find any "compensatory" increase in other causes of death among lean women after adequately accounting for premenorbid weight loss and confounding by cigarette smoking.22

In conclusion, these data add to the already voluminous evidence that excess body fat is a cause of CHD. They also clearly indicate that even modest gains in weight during adult life and levels of body weight not generally considered to be overweight are associated with important increases in risk of CHD. Although the magnitude of RRs associated with excess adiposity are lower than those associated with cigarette smoking, the proportion of cases attributable to these two causes is similar because most middle-aged US women have body weights above those associated with the lowest rates of CHD. Furthermore, the data strongly suggest that the 1990 weight goals set by the National Institutes of Health, Dr. Manson is the recipient of a Merck/Society for Epidemiologic Research grant award.

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References