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## BODY WEIGHT AND MORTALITY AMONG WOMEN

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**Abstract Background.** *The relation between body weight and overall mortality remains controversial despite considerable investigation.*

**Methods.** *We examined the association between body-mass index (defined as the weight in kilograms divided by the square of the height in meters) and both overall mortality and mortality from specific causes in a cohort of 115,195 U.S. women enrolled in the prospective Nurses' Health Study. These women were 30 to 55 years of age and free of known cardiovascular disease and cancer in 1976. During 16 years of follow-up, we documented 4726 deaths, of which 881 were from cardiovascular disease, 2586 from cancer, and 1259 from other causes.*

**Results.** *In analyses adjusted only for age, we observed a J-shaped relation between body-mass index and overall mortality. When women who had never smoked were examined separately, no increase in risk was observed among the leaner women, and a more direct relation between weight and mortality emerged ( $P$  for trend  $< 0.001$ ). In multivariate analyses of women who had never smoked and had recently had stable weight, in which the first four years of follow-up were excluded, the relative risks of death from all causes for increasing categories*

*of body-mass index were as follows: body-mass index  $< 19.0$  (the reference category), relative risk = 1.0; 19.0 to 21.9, relative risk = 1.2; 22.0 to 24.9, relative risk = 1.2; 25.0 to 26.9, relative risk = 1.3; 27.0 to 28.9, relative risk = 1.6; 29.0 to 31.9, relative risk = 2.1; and  $\geq 32.0$ , relative risk = 2.2 ( $P$  for trend  $< 0.001$ ). Among women with body-mass indexes of 32.0 or higher who had never smoked, the relative risk of death from cardiovascular disease was 4.1 (95 percent confidence interval, 2.1 to 7.7), and that of death from cancer was 2.1 (95 percent confidence interval, 1.4 to 3.2), as compared with the risk among women with body-mass indexes below 19.0. A weight gain of 10 kg (22 lb) or more since the age of 18 was associated with increased mortality in middle adulthood.*

**Conclusions.** *Body weight and mortality from all causes were directly related among these middle-aged women. Lean women did not have excess mortality. The lowest mortality rate was observed among women who weighed at least 15 percent less than the U.S. average for women of similar age and among those whose weight had been stable since early adulthood. (N Engl J Med 1995;333:677-85.)*

**T**HE relation between body weight and mortality remains a subject of intense debate, particularly with respect to the optimal weight for longevity. Although severe obesity is clearly associated with increased mortality,<sup>1</sup> the health consequences of being mildly to moderately overweight remain controversial. Furthermore, leanness has been linked to elevated

mortality in several studies, but the validity of this finding remains in dispute. Diverse findings concerning the nature of the relation between weight and mortality have included no association,<sup>2-5</sup> a J-shaped<sup>2,4,6-9</sup> or U-shaped<sup>10,11</sup> relation, a direct association,<sup>5,12-15</sup> and an inverse association.<sup>16</sup>

Although the biologic plausibility of adverse effects of obesity on mortality from cardiovascular causes<sup>1,17</sup> and from cancer<sup>1,7</sup> is well established, no cogent evidence supports deleterious consequences of leanness with respect to the major causes of death in industrialized countries. The absence of a direct relation between body weight and mortality in many studies may result instead from methodologic limitations.<sup>13,18</sup> As we have stated previously, such limitations include the failure to account for cigarette smoking, which is more prevalent among relatively lean persons and is a major independent risk factor for death; the failure to eliminate bias due to preexisting disease and illness-related weight loss; and inappropriate control for the biologic effects

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of obesity, such as hypertension and hyperglycemia.<sup>18</sup> In a review of previous prospective studies of body weight and mortality, we found that each one had at least one of these shortcomings.<sup>18</sup>

The importance of understanding the true association between weight and mortality is underscored by the increasing prevalence of obesity in the United States,<sup>19,20</sup> especially among women.<sup>21</sup> Thirty-two million women and 26 million men (approximately one third of the U.S. adult population) are overweight — i.e., weigh at least 20 percent more than “desirable” levels.<sup>20</sup> National survey data suggest that, in the past 15 years, the mean body weight of U.S. adults has increased by 3.6 kg (7.9 lb).<sup>20</sup> Concurrently, recommended weight standards have become increasingly permissive over the past several decades. The 1990 U.S. weight guidelines<sup>22</sup> list weights that are up to 9 kg (20 lb) higher for some heights than those listed in the 1959 Metropolitan Life Insurance Company tables<sup>23</sup>; the 1990 guidelines recommend values for body-mass index (the weight in kilograms divided by the square of the height in meters) that range from 21 to 27. Furthermore, weight gains of up to 9 kg after 35 years of age are sanctioned as falling within the desirable guidelines.<sup>22</sup>

We examined the relation between body-mass index and both overall mortality and mortality from specific causes in a large cohort of middle-aged women enrolled in the prospective Nurses' Health Study. We also assessed the role of weight gain since the age of 18 and the ratio of waist circumference to hip circumference in predicting mortality in the cohort. We took into account the methodologic limitations described above and assessed whether the present data support the increasingly higher recommended weights.

## METHODS

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses 30 to 55 years of age who lived in 1 of 11 states responded to questionnaires requesting information about their medical history and health behavior.<sup>24,25</sup> The participants in the investigation we describe here were the 115,195 women who were free of diagnosed cardiovascular disease and cancer in 1976 and who provided data on their height and weight. On the basis of a subsample of 249 participants, we estimate that 98 percent of the cohort is white.

### Risk Factors

The 1976 questionnaire included questions about age, current weight and height, current and past cigarette smoking, other risk factors, and medical history.<sup>25</sup> Questionnaires mailed every two years requested information on these variables and on newly diagnosed major illnesses. In 1980, participants were asked to provide their weight at the age of 18; a semiquantitative food-frequency questionnaire and questions concerning physical activity were also included.

### End Points

Deaths among study participants were identified through searches of state vital records and the National Death Index, as well as from reports by next of kin and postal authorities. We estimate that more than 98 percent of the deaths in this cohort have been identified.<sup>26</sup> We obtained copies of death certificates and medical records, when

available, and determined causes of death (classified according to the categories of the *International Classification of Diseases, Eighth Revision* [ICD-8]). The primary end point in the present analyses was overall mortality after study entry in 1976, with follow-up through 1992. We also examined deaths due to coronary heart disease (ICD codes 410 through 414), cardiovascular disease (codes 390 through 459 and 795), cancer (codes 140 through 207), and other causes. Criteria for deaths due to coronary disease, cardiovascular disease, and cancer have been reported previously.<sup>24,25</sup>

## Validation Studies

### Reported Weight

In a validation study of the weights reported by the participants, a subsample consisting of 184 women was chosen, and the women were weighed 6 to 12 months after completing the mailed questionnaire. Reported weights were highly correlated with measured weights (Spearman  $r=0.96$ ), although they averaged 1.5 kg (3.3 lb) lower than the measured values.<sup>27</sup>

### Body-Mass Index

Body-mass index was used as a measure of obesity. This index is independent of height ( $r=-0.03$ ) and strongly related to weight ( $r=0.86$ ).<sup>28</sup> The body-mass-index categories for our analyses were as follows: <19.0, 19.0 to 21.9, 22.0 to 24.9, 25.0 to 26.9, 27.0 to 28.9, 29.0 to 31.9, and  $\geq 32.0$ . These categories correspond approximately to percentiles 0 to 14, 15 to 29, 30 to 54, 55 to 64, 65 to 74, 75 to 89, and 90 to 100 of the body-mass index among middle-aged U.S. women.<sup>29</sup> Expressed as a percentage of desirable weight according to the Metropolitan Life Insurance Company Tables of 1983, these categories correspond approximately to <90 percent, 90 to 99 percent, 100 to 114 percent, 115 to 119 percent, 120 to 129 percent, 130 to 139 percent, and  $\geq 140$  percent of recommended weights.<sup>30</sup> Participants in the Nurses' Health Study cohort weighed, on average, 3 kg (6.6 lb) less than women of similar age in the general U.S. population.<sup>29</sup>

### Weight at 18 Years of Age

On the 1980 questionnaire, participants were asked to record their weight at the age of 18. A validation study of recalled weight at age 18 was conducted in a second cohort of nurses, the Nurses' Health Study II. Pearson correlation coefficients ( $r$ ) for reported and actual weights were 0.87 for weight at the age of 18 and 0.84 for body-mass index at the age of 18.<sup>31</sup>

### Waist and Hip Circumference

On the 1986 questionnaire, participants were asked to measure their waist circumference (at the umbilicus) and hip circumference (at the largest point) using a tape measure and to report the values. In a validation study, crude Pearson correlation coefficients for reported and measured circumferences were 0.89 for the waist, 0.84 for the hip, and 0.70 for the waist-to-hip ratio.<sup>32</sup>

## Statistical Analysis

The study subjects were grouped according to seven categories of body-mass index, based on their reported height and weight on the 1976 questionnaire. Deaths were assigned to the body-mass-index category at base line, with the follow-up period dating from the return of the questionnaire to the date of death or June 1, 1992, whichever came first. As noted earlier, women who reported having cardiovascular disease or cancer in 1976 were excluded. Mortality rates were calculated by dividing the number of deaths by the cumulated number of person-years of follow-up for a given body-mass-index category. For analyses in which we controlled for alcohol consumption, physical activity, and dietary fat intake and those focusing on weight at the age of 18, follow-up dated from the return of the 1980 questionnaire, when this information was first requested. Similarly, for analyses in which the first four years of follow-up were excluded, follow-up was calculated from 1980 to 1992.

The relative risk, computed as the mortality rate in a specific cat-

egory of body-mass index divided by the corresponding rate in the leanest category (body-mass index <19.0), was used as a measure of the strength of association. The percentage of attributable risk (the difference between these two incidence rates divided by the incidence rate in each category, times 100 percent) served as an estimate of the proportion of deaths in each category that were attributable to adiposity.<sup>33</sup> The Mantel extension test was used to assess overall trends, and proportional-hazards models controlled for multiple risk factors simultaneously.<sup>34</sup> We calculated the 95 percent confidence intervals for each relative risk and two-sided P values for the Mantel extension test for linear trend.<sup>34</sup>

## RESULTS

During the 16 years of observation, we identified 4726 deaths, of which 881 were from cardiovascular disease, 2586 from cancer, and 1259 from other causes. The cohort for this study consisted of the 115,195 women who were free of cardiovascular disease and cancer at entry; 1,798,993 person-years of follow-up were accrued in this cohort.

The distribution of several risk factors for death varied according to the category of body-mass index in this cohort.<sup>35</sup> Body-mass index was inversely related to smoking status; current smokers constituted 43.8 percent of the leanest group but only 23.3 percent of the heaviest. Alcohol consumption, postmenopausal hormone use, and regular, vigorous exercise were also more common among leaner women. Reported hypertension, diabetes, and elevated serum cholesterol levels

were two to six times more prevalent among women in the heavier categories. Dietary intake of fat and its subtypes, as well as dietary cholesterol intake, however, varied minimally in relation to body-mass-index category.

In age-adjusted analyses, we observed a *J*-shaped relation between body-mass index and overall mortality (Table 1). Mortality was lowest among women with body-mass indexes from 19.0 through 26.9. Multivariate adjustment for smoking and other risk factors strengthened the association between obesity and mortality but did not materially alter the shape of the curve.

When women who had never smoked were examined separately, a more direct relation between body-mass index and mortality emerged (Table 1). No evidence of a *J*-shaped or *U*-shaped association persisted in these analyses, and the results were not changed materially after multivariate adjustment. A comparison of the shapes of the curves for women who had never smoked, former smokers, and current smokers is presented in Figure 1. For former and current smokers, the relation between weight and mortality remained *J*-shaped. Multivariate control for the number of cigarettes smoked per day, the duration of smoking, and the length of time since quitting (for former smokers) did not materially alter these associations. For women who

Table 1. Body-Mass Index and Relative Risk of Death from All Causes among Women Who Were 30 to 55 Years of Age in 1976 and Were Followed from 1976 through 1992.\*

| VARIABLE  | BODY-MASS INDEX |           |           |           |           |           |          | P FOR TREND |
|---|-----------------|-----------|-----------|-----------|-----------|-----------|----------|-------------|
|   | <19.0           | 19.0–21.9 | 22.0–24.9 | 25.0–26.9 | 27.0–28.9 | 29.0–31.9 | ≥32.0    |             |
| No. of women  | 14,771          | 31,992    | 36,187    | 12,558    | 7,394     | 6,825     | 5,468    |             |
| Mean weight — lb (kg)   | 113 (51)        | 125 (56)  | 138 (63)  | 154 (70)  | 165 (75)  | 178 (81)  | 210 (95) |             |
| Mean BMI  | 18.7            | 21.1      | 23.4      | 25.9      | 27.9      | 30.3      | 35.8     |             |
| <b>All women</b>  |                 |           |           |           |           |           |          |             |
| No. of deaths   | 577             | 1,054     | 1,392     | 512       | 385       | 413       | 393      |             |
| Person-years of follow-up   | 230,899         | 501,081   | 565,551   | 196,254   | 114,883   | 105,803   | 84,522   |             |
| Age-adjusted RR†  | 1.0             | 0.8       | 0.8       | 0.7       | 0.9       | 1.1       | 1.3      | 0.001       |
| Multivariate RR‡  | 1.0             | 0.8       | 0.8       | 0.8       | 1.0       | 1.2       | 1.5      | <0.001      |
| 95% CI  | —               | 0.7–0.9   | 0.7–0.9   | 0.7–0.9   | 0.9–1.1   | 1.0–1.3   | 1.3–1.7  |             |
| <b>Women who never smoked</b>                                     |                 |           |           |           |           |           |          |             |
| No. of deaths   | 111             | 297       | 439       | 175       | 146       | 174       | 157      |             |
| Person-years of follow-up   | 87,278          | 205,336   | 245,772   | 89,728    | 54,720    | 52,019    | 42,640   |             |
| Age-adjusted RR†  | 1.0             | 1.0       | 1.1       | 1.1       | 1.4       | 1.8       | 1.9      | <0.001      |
| Multivariate RR‡  | 1.0             | 1.0       | 1.1       | 1.1       | 1.4       | 1.7       | 1.9      | <0.001      |
| 95% CI  | —               | 0.8–1.3   | 0.9–1.3   | 0.8–1.3   | 1.1–1.8   | 1.4–2.2   | 1.5–2.5  |             |
| <b>Women who never smoked and had recently had stable weight§</b> |                 |           |           |           |           |           |          |             |
| No. of deaths   | 46              | 136       | 172       | 56        | 42        | 46        | 33       |             |
| Person-years of follow-up   | 42,765          | 96,096    | 95,084    | 27,491    | 15,181    | 12,581    | 8,812    |             |
| Age-adjusted RR†  | 1.0             | 1.2       | 1.3       | 1.2       | 1.5       | 2.1       | 2.2      | <0.001      |
| Multivariate RR¶  | 1.0             | 1.2       | 1.2       | 1.3       | 1.6       | 2.1       | 2.2      | <0.001      |
| 95% CI  | —               | 0.8–1.6   | 0.9–1.7   | 0.9–1.9   | 1.1–2.5   | 1.4–3.2   | 1.4–3.4  |             |

\*The body-mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. RR denotes relative risk (as compared with the leanest women), and CI confidence interval.

†Adjusted for age in five-year categories.

‡Adjusted for age in five-year categories, smoking (never, former, or current [1 to 14, 15 to 24, or ≥25 cigarettes per day]), menopausal status, oral-contraceptive and postmenopausal hormone use (never, past, or current), and parental history of myocardial infarction before the age of 60 (yes or no).

§Limited to women with stable weight (weight change <4 kg [8.8 lb]) from 1976 to 1980 and excluding the first four years of follow-up.

¶Adjusted for all the variables in the above multivariate model, plus alcohol intake (in five categories), saturated-fat intake (in quintiles), and physical activity (in five categories).

had never smoked, mortality was lowest at body-mass indexes below 22.0.

To assess the potential effect of bias due to preexisting disease and illness-related weight loss, we performed separate analyses for early mortality (1976 through 1980) and excluding the first four years of follow-up (i.e., including only 1980 to 1992) among the women who had never smoked. For the early period, we observed no association between body-mass index and mortality ( $P$  for trend = 0.18). In contrast, for the period 1980 through 1992, a direct association was observed between the body-mass index in 1976 and mortality from all causes; mortality was lowest among women with body-mass indexes below 19.0 (Fig. 2, lower left). Additional control for alcohol intake, physical activity, and saturated-fat intake (first determined on the 1980 questionnaire) did not change these relative risks.

To address more fully the effect of potential bias due to recent weight loss and fluctuations in weight, we conducted an additional analysis limited to women who

had never smoked and had had stable weight (weight change, less than 4 kg [8.8 lb]) in the previous four years (1976 through 1980) (Table 1 and Fig. 2, lower right). For the follow-up period 1980 through 1992, the corresponding multivariate relative risks among women who never smoked, according to body-mass-index category and as compared with the women with a body-mass index below 19.0, were as follows: body-mass index <19.0, relative risk = 1.0; 19.0 to 21.9, relative risk = 1.2; 22.0 to 24.9, relative risk = 1.2; 25.0 to 26.9, relative risk = 1.3; 27.0 to 28.9, relative risk = 1.6; 29.0 to 31.9, relative risk = 2.1; and  $\geq 32.0$ , relative risk = 2.2 ( $P$  for trend <0.001). Again, mortality was lowest among women with a body-mass index below 19.0; mortality among obese women (body-mass index,  $\geq 29.0$ ) was more than twice that among the leanest women. In terms of attributable risk, 53 percent of the deaths among the women with a body-mass index of 29.0 or higher could be attributed to their obesity. Even after further control for hypertension, diabetes, and high cholesterol, which reflect the biologic effects

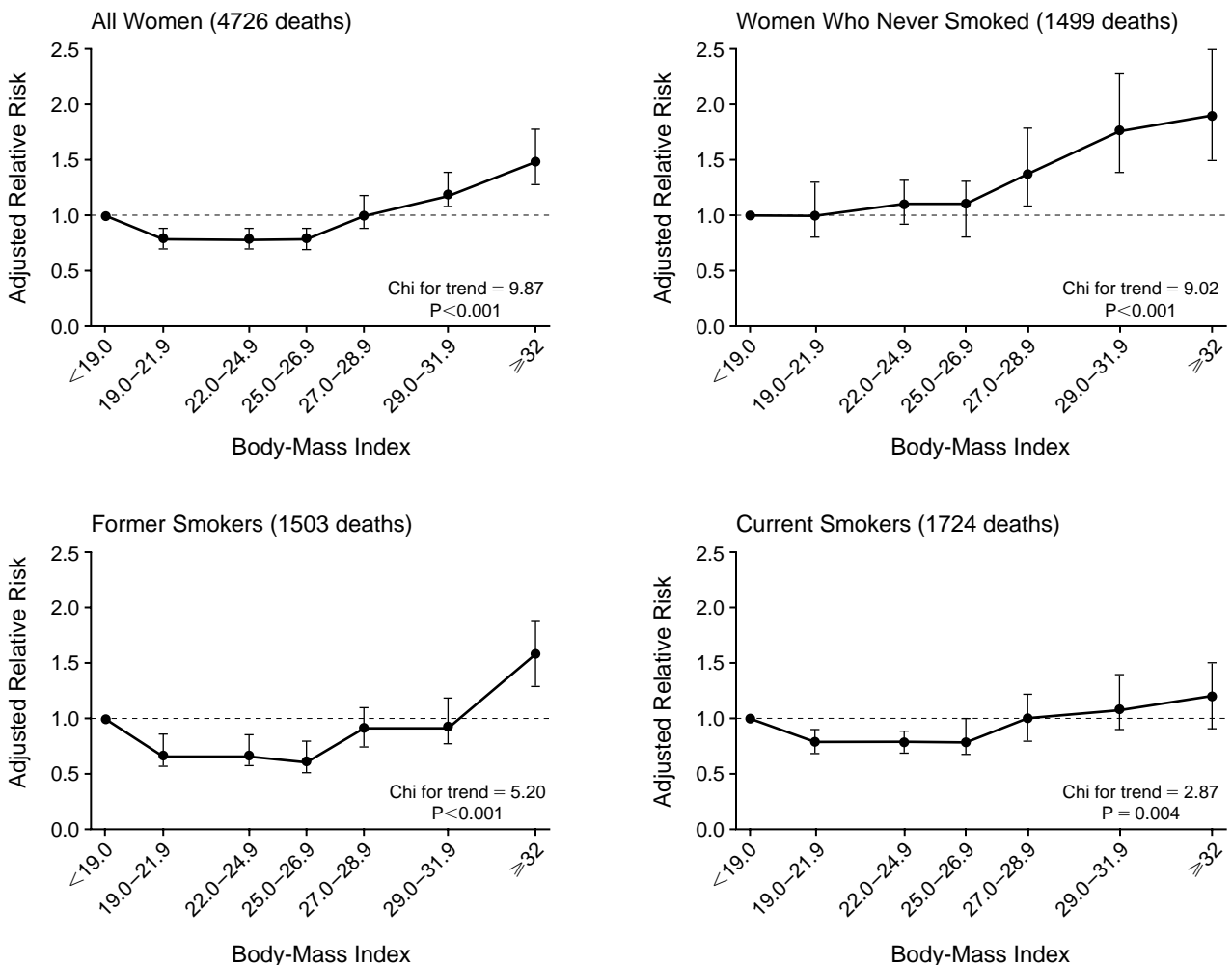


Figure 1. Relative Risk of Death from All Causes, 1976 through 1992, According to Body-Mass Index, for All Women, Women Who Never Smoked, Former Smokers, and Current Smokers.

All relative risks have been adjusted for age in five-year categories. For the total cohort and for current smokers, relative risks have been additionally adjusted for the intensity of smoking (1 to 14, 15 to 24, or  $\geq 25$  cigarettes per day). The bars represent 95 percent confidence intervals. In all cases, the reference category is the women with a body-mass index below 19.0.

of obesity and can be considered intermediate steps in the causal pathway, mortality was lowest among the leanest women (the corresponding multivariate relative risks for the increasing levels of body-mass index studied were 1.0, 1.2, 1.2, 1.2, 1.5, 1.8, and 1.7;  $P$  for trend = 0.005).

In analyses of disease-specific mortality among women who had never smoked, body-mass index was positively related to the risk of death from cardiovascular disease, cancer, and other causes (Fig. 3). Rates of death due to cardiovascular disease among the obese women (body-mass index,  $\geq 29.0$ ) were four times higher than those among the leanest women. For deaths due to coronary heart disease, the relative risks for the increasing levels of body-mass index studied were 1.0,

1.0, 1.4, 1.7, 3.1, 4.6, and 5.8 ( $P$  for trend  $< 0.001$ ). Rates of death due to cancer among obese women were double those for the leanest women, predominantly because of increased mortality due to colon, breast, and endometrial cancers.

We observed no evidence of a modifying effect of age in these analyses, and no evidence that the lowest mortality occurred at higher weights among the older participants. Similar results were observed for women in each of the age groups studied in this cohort, although the statistical power of such subgroup analyses was limited.

We next examined the role of weight change during adulthood in relation to overall and cause-specific mortality in the cohort (Table 2). A weight gain of 10 kg

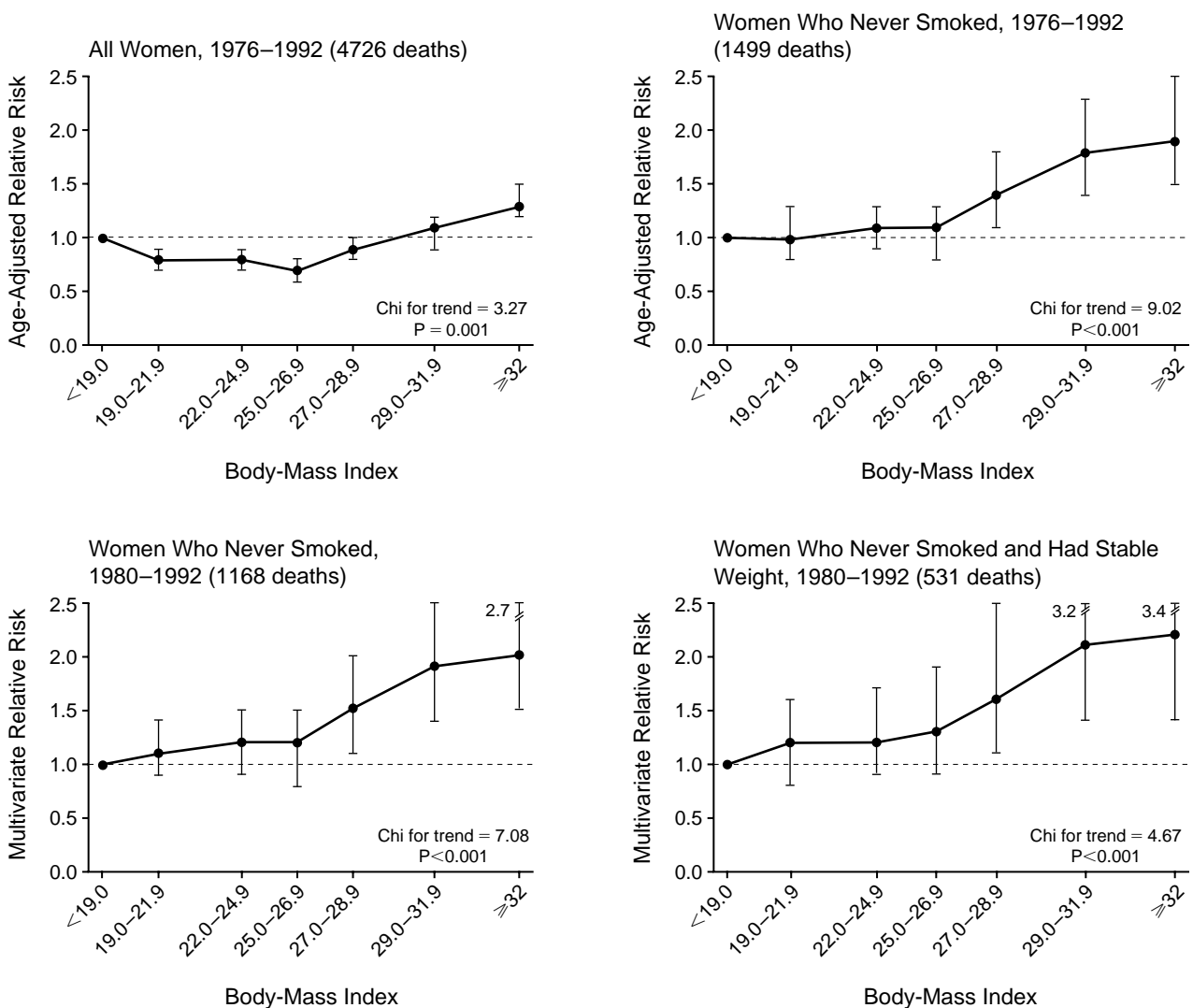


Figure 2. The Influence of Increasing Control for Methodologic Bias on the Shape of the Curve Describing the Relation between Body-Mass Index and the Relative Risk of Death from All Causes.

The curve progressed from a J shape in age-adjusted analyses of the entire cohort (upper left) to an increasingly direct association when the analysis was restricted to women who never smoked (upper right), when early deaths were excluded (lower left), and when only women with stable weight in the previous four years were included (lower right). The multivariate models included age, smoking status, menopausal status, oral-contraceptive and postmenopausal hormone use, and parental history of myocardial infarction before the age of 60 (lower left) and these variables plus alcohol intake, saturated-fat intake, and physical activity (lower right). The bars represent 95 percent confidence intervals. In all cases, the reference category is the women with a body-mass index below 19.0.

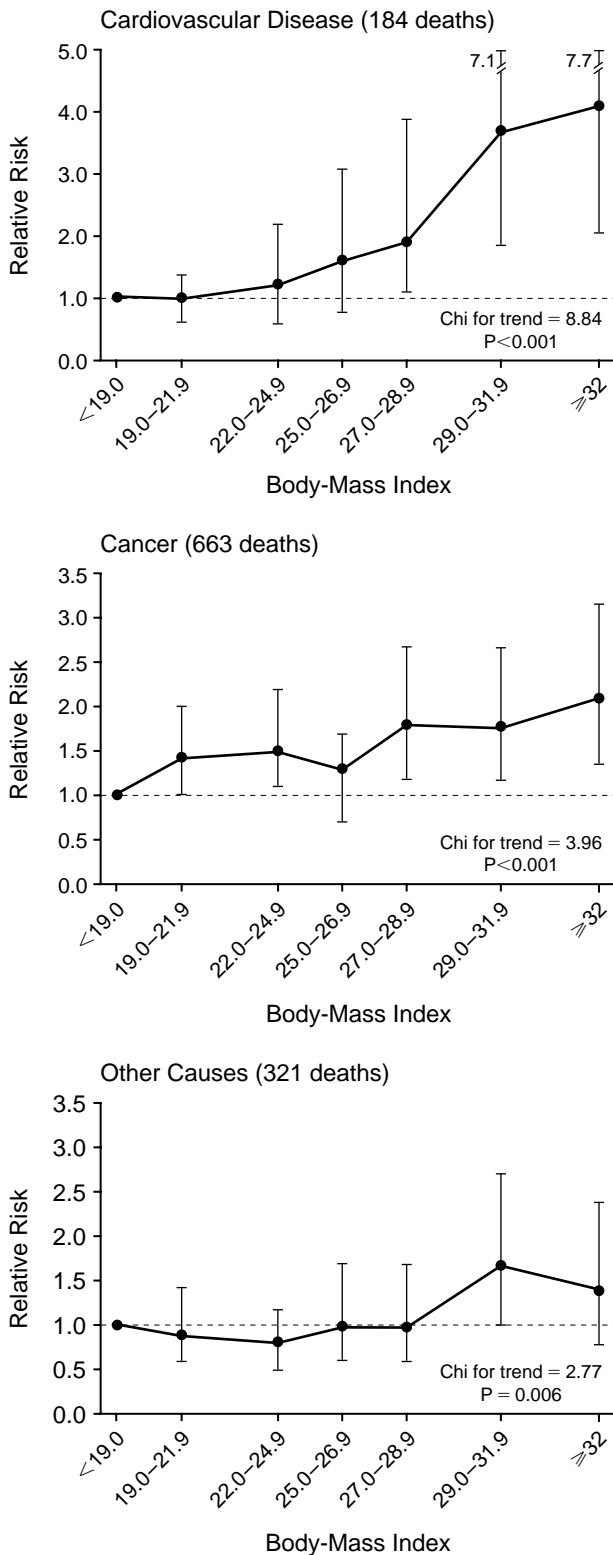


Figure 3. Relative Risk of Death from Cardiovascular Disease, Cancer, and Other Causes, According to Body-Mass Index among Women Who Never Smoked.

The follow-up period was 1980 through 1992 (i.e., excluding the first four years of follow-up). Deaths from cardiovascular disease include those due to coronary heart disease, stroke, and other cardiovascular causes. All relative risks have been adjusted for age in five-year categories. The bars represent 95 percent confidence intervals. In each case, the reference category is the women with a body-mass index below 19.0.

(22 lb) or more since the age of 18 was associated with increased mortality in middle adulthood. In contrast, women who had lost weight or gained less than 10 kg did not have significant changes in mortality. The body-mass index at the age of 18 was also a predictor of mortality due to cardiovascular disease and of overall mortality in middle adulthood (Fig. 4).

The association between the waist-to-hip ratio and mortality from all causes from 1986 through 1992 was weaker than that between the body-mass index and mortality (among women who had never smoked, the age-adjusted relative risks of death for increasing quintiles of the waist-to-hip ratio were 1.0, 1.1, 1.3, 1.3, and 1.4; P for trend = 0.08). In contrast, the waist-to-hip ratio was a strong predictor of death due to coronary heart disease in this cohort (relative risk for increasing quintiles of the ratio, 1.0, 2.8, 2.2, 3.7, and 8.7; P for trend = 0.04).

## DISCUSSION

These prospective data support a direct association between body-mass index and mortality among women, after cigarette smoking and disease-related weight loss were taken into account. In the optimal analyses — limited to women who had never smoked and had recently had stable weight — the lowest mortality was among the leanest women (those with a body-mass index below 19.0), weighing at least 15 percent below average U.S. weights for middle-aged women. We observed no evidence of a J-shaped curve or of increased mortality in the leanest group of women. Mortality among the obese women (body-mass index,  $\geq 29.0$ ) was more than twice that among the leanest women. Although mortality did not increase substantially until the body-mass index reached 27.0, a trend toward higher mortality due to coronary heart disease and other cardiovascular diseases, as well as cancer, was apparent even among women at average weights and those who were mildly overweight. Furthermore, body-mass indexes of 22.0 or higher at 18 years of age were associated with a significant elevation in subsequent mortality from cardiovascular disease; a weight gain of 10 kg or more since the age of 18 predicted increased mortality due to cardiovascular disease, cancer, and all causes. The body-mass index was a stronger predictor of mortality in this cohort than was the waist-to-hip ratio.

When former and current smokers were analyzed separately, a J-shaped association between body-mass index and mortality persisted in these subgroups. The slight excess mortality among the leanest women (body-mass index,  $< 19.0$ ) in these subgroups may represent a true adverse interaction between smoking and leanness, but it is more likely to reflect residual confounding by the intensity and duration of smoking.

Because hypertension, diabetes, and hypercholesterolemia are biologic effects of obesity<sup>1,17</sup> and are intermediate steps in the causal pathway linking obesity to increased mortality due to cardiovascular disease,<sup>18,35</sup> we did not control for these variables in our primary multivariate models. When we included these variables in a separate multivariate analysis, the relation between

Table 2. Weight Change since the Age of 18 and Relative Risk of Death from All Causes and from Specific Diseases among Women Who Never Smoked, 1980 through 1992.\*

| WEIGHT CHANGE          | NO. OF DEATHS | relative risk (95% confidence interval) |                        |                        |               |
|------------------------|---------------|---|------------------------|------------------------|---------------|
|                        |               | ALL CAUSES                              | CORONARY HEART DISEASE | CARDIOVASCULAR DISEASE | CANCER        |
| Loss                   |               |   |                        |                        |               |
| ≥10 kg                 | 16            | 0.7 (0.4–1.4)                           | 0.3 (0.0–4.3)          | 1.0 (0.3–3.7)          | 0.9 (0.4–1.9) |
| 4–9 kg                 | 54            | 1.2 (0.9–1.6)                           | 0.6 (0.1–3.3)          | 1.7 (0.8–3.5)          | 1.1 (0.7–1.6) |
| Stable (change, <4 kg) | 224           | 1.0                                     | 1.0                    | 1.0                    | 1.0           |
| Gain                   |               |   |                        |                        |               |
| 4–9 kg                 | 269           | 1.0 (0.8–1.2)                           | 0.7 (0.4–1.8)          | 0.8 (0.4–1.4)          | 1.2 (0.9–1.5) |
| 10–19 kg               | 292           | 1.2 (1.0–1.4)                           | 2.6 (0.7–12.8)         | 1.7 (1.1–2.8)          | 1.2 (0.9–1.5) |
| ≥20 kg                 | 204           | 1.6 (1.3–1.9)                           | 7.4 (2.4–21.7)         | 3.3 (2.1–5.2)          | 1.5 (1.1–1.9) |
| P for trend            |               | <0.001                                  | 0.002                  | <0.001                 | 0.009         |

\*Relative risks are for women in the specified weight-change category as compared with those with stable weight. They have been adjusted for age in five-year groups and for body-mass index at the age of 18 (in seven categories). To convert values in kilograms to pounds, multiply by 2.2.

body-mass index and mortality was attenuated, as expected, but not eliminated.

The prospective design of this study has the advantage of minimizing bias due to differences in the reporting of weight as a result of morbidity. Women with diagnosed cardiovascular disease and cancer were excluded at base line. The exclusion of the first four years of follow-up in the analyses of weight and mortality and the long duration of follow-up would be expected to reduce the potential for bias caused by the presence of subclinical disease at entry and by illness-related weight loss. Other advantages of this cohort study include its large size and large number of end points, the high follow-up rate, and the large number of potential confounders for which data were collected.

Limitations of the present study must also be considered. Weights and heights were not measured but were instead reported by the participants. In an internal validation study, however, the reported weights were found to be highly reliable (Spearman  $r=0.96$  for the correlation between reported and measured weights).<sup>27,32</sup> In contrast, waist and hip measurements were reported somewhat less reliably,<sup>32</sup> and misclassification due to inaccurate reporting could have attenuated true associations between the waist-to-hip ratio and mortality from all causes. Moreover, only six years of follow-up were available for the analyses including waist and hip circumferences.

Although our study population of registered nurses is not representative of the general U.S. population, the relative homogeneity of the cohort may actually enhance the study's internal validity. Because of the relatively uniform educational attainment and socioeconomic status of the women in the cohort, confounding by these variables is unlikely to pose a substantial problem.

Prospective data on body weight and mortality among women have been limited.<sup>2-12,16</sup> In most studies, either no association<sup>2-5</sup> or a J-shaped or U-shaped relation<sup>6-11</sup> has been observed. Only two studies have shown a direct, positive relation.<sup>5,12</sup> In only two studies of women, however, were women who had never smoked analyzed separately.<sup>7,9</sup> In the American Cancer

Society cohort,<sup>7</sup> a nearly direct association between weight and mortality was observed among women who had never smoked, with the lowest mortality among women at 80 to 89 percent of the average weight for the cohort. A slight elevation in mortality was observed among women with weights below 80 percent of the average, but subclinical disease and early mortality were not excluded in these analyses. In the Iowa Women's Health Study, a J-shaped relation between body-mass index and mortality was observed among women who had never smoked, with the lowest mortality observed among women in the third quintile of body-mass index.<sup>9</sup> However, only five-year fol-

low-up data were available for these analyses; thus, the effects of subclinical disease and early mortality could not be adequately eliminated. Notably, during our first four years of follow-up, a period similar to that studied in the Iowa cohort,<sup>9</sup> we also observed little relation between body-mass index and mortality. Other studies of women have been limited not only by the absence of an analysis of women who never smoked but also by small size and insufficient power to detect associations<sup>3,4,16</sup> and by failure to account for underlying disease.<sup>5,7,9,10,12,16</sup>

In the cohort we studied, body-mass index was more strongly associated with deaths due to coronary heart disease and other cardiovascular diseases than with deaths due to other causes. Because deaths due to cardiovascular causes constituted less than one fifth of those in the cohort, the end point of overall mortality was largely diluted by deaths from causes that bore no material relation to body weight. An even stronger association between weight and mortality could be expected in the general population, in which deaths due to cardiovascular disease constitute a larger proportion of all deaths. Although overall mortality was substantially elevated only among women whose body-mass index was 27.0 or higher, deaths due to coronary disease were increased among women with a body-mass index of 22.0 or more. Furthermore, several important causes of morbidity in this cohort were directly related to body weight; the risks of nonfatal myocardial infarction,<sup>35,36</sup> diabetes,<sup>37</sup> hypertension,<sup>38</sup> and gallstones<sup>39</sup> were greater, not only among the obese women but also among women who were of average weight or mildly overweight, than among their leaner peers. A recent report from the Framingham Offspring Study suggested that the prevalence of risk factors for cardiovascular disease rises rapidly at body-mass indexes above 20.<sup>40</sup>

In conclusion, these prospective data indicate that body weight is an important determinant of mortality among middle-aged women. The apparent excess risks associated with leanness were found to be artifactual in this study and were eliminated after we accounted for cigarette smoking and subclinical disease. Among

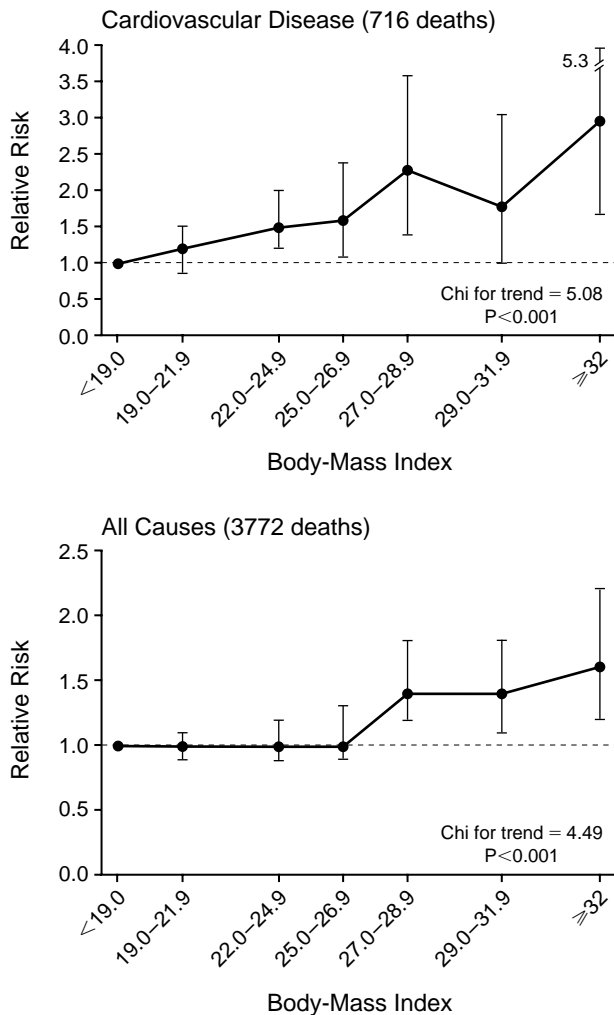


Figure 4. Relative Risk of Death Due to Cardiovascular Disease and Death from All Causes, According to Body-Mass Index at the Age of 18.

The follow-up period was 1980 through 1992, since weight at 18 years was first ascertained in 1980. Deaths from cardiovascular disease include those due to coronary heart disease, stroke, and other cardiovascular causes. All relative risks have been adjusted for age (in five-year categories) and for the intensity of smoking (1 to 14, 15 to 24, or  $\geq 25$  cigarettes per day). The bars represent 95 percent confidence intervals. In both cases, the reference category is the women with body-mass indexes below 19.0.

women who had never smoked, the leanest women in the cohort (those with body-mass indexes below 19.0) had the lowest mortality, and even women with average weights had higher mortality. Mortality was lowest among women whose weights were below the range of recommended weights in the current U.S. guidelines. Moreover, a weight gain of 10 kg or more since the age of 18 was associated with increased mortality in middle adulthood. These data indicate that the lowest mortality rate for U.S. middle-aged women is found at body weights at least 15 percent below the U.S. average for women of similar age. The increasingly permissive U.S. weight guidelines may therefore be unjustified and potentially harmful.

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## REFERENCES

1. Van Itallie TB. Obesity: adverse effects on health and longevity. *Am J Clin Nutr* 1979;32:Suppl:2723-33.
2. Schroll M. A longitudinal epidemiological survey of relative weight at age 25, 50 and 60 in the Glostrup population of men and women born in 1914. *Dan Med Bull* 1981;28:106-16.
3. Tuomilehto J, Salonen JT, Marti B, et al. Body weight and risk of myocardial infarction and death in the adult population of eastern Finland. *BMJ* 1987;295:623-7.
4. Vandembroucke JP, Mauritz BJ, de Bruin A, Verheesen JHH, van der Heide-Wessel C, van der Heide RM. Weight, smoking, and mortality. *JAMA* 1984;252:2859-60.
5. Stevens J, Keil JE, Rust PF, Tyroler HA, Davis CE, Gazes PC. Body mass index and body girths as predictors of mortality in black and white women. *Arch Intern Med* 1992;152:1257-62.
6. Comstock GW, Kendrick MA, Livesay VT. Subcutaneous fatness and mortality. *Am J Epidemiol* 1966;83:548-63.
7. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *J Chronic Dis* 1979;32:563-76.
8. Build Study 1979. Chicago: Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980.
9. Folsom AR, Kaye SA, Sellers TA, et al. Body fat distribution and 5-year risk of death in older women. *JAMA* 1993;269:483-7.
10. Waaler HT. Height, weight and mortality: the Norwegian experience. *Acta Med Scand Suppl* 1984;679:1-56.
11. Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L. Body mass index and mortality among nonsmoking older persons: the Framingham Heart Study. *JAMA* 1988;259:1520-4.
12. Build and Blood Pressure Study 1959. Chicago: Society of Actuaries, 1959.
13. Garrison RJ, Feinleib M, Castelli WP, McNamara PM. Cigarette smoking as a confounder of the relationship between relative weight and long-term mortality: the Framingham Heart Study. *JAMA* 1983;249:2199-203.
14. Linsted K, Tonstad S, Kuzma JW. Body mass index and patterns of mortality among Seventh-day Adventist men. *Int J Obes* 1991;15:397-406.
15. Lee I-M, Manson JE, Hennekens CH, Paffenbarger RS Jr. Body weight and mortality: a 27-year follow-up of middle-aged men. *JAMA* 1993;270:2823-8.
16. Wilcosky T, Hyde J, Anderson JJB, Bangdiwala S, Duncan B. Obesity and mortality in the Lipid Research Clinics Program Follow-up Study. *J Clin Epidemiol* 1990;43:743-52.
17. Mann GV. The influence of obesity on health. *N Engl J Med* 1974;291:178-85, 226-32.
18. Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: a reassessment. *JAMA* 1987;257:353-8.
19. Health implications of obesity: National Institutes of Health Consensus Development Conference Statement. *Ann Intern Med* 1985;103:1073-7.
20. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among U.S. adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 1994;272:205-11.
21. Harlan WR, Landis JR, Flegal KM, Davis CS, Miller ME. Secular trends in body mass in the United States, 1960-1980. *Am J Epidemiol* 1988;128:1065-74.
22. Department of Agriculture, Department of Health and Human Services. Nutrition and your health: dietary guidelines for Americans. 3rd ed. Washington, D.C.: Government Printing Office, 1990.
23. New weight standards for men and women. *Stat Bull Metrop Insur Co* 1959;40 (November-December):1-4.
24. Hennekens CH, Speizer FE, Rosner B, Bain CJ, Belanger C, Peto R. Use of permanent hair dyes and cancer among registered nurses. *Lancet* 1979;1:1390-3.
25. Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med* 1985;313:1044-9.
26. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol* 1984;119:837-9.
27. Willett WC, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983;117:651-8.
28. Romieu I, Willett WC, Stampfer MJ, et al. Energy intake and other determinants of relative weight. *Am J Clin Nutr* 1988;47:406-12.
29. National Center for Health Statistics, Najjar MF, Rowland M. Anthropometric reference data and prevalence of overweight, United States, 1976-80. Vital and health statistics. Series 11. No. 238. Washington, D.C.: Government Printing Office, 1987. (DHHS publication no. (PHS) 87-1688.)
30. 1983 Metropolitan height and weight tables. *Stat Bull Metrop Insur Co* 1983;64:2-9.

31. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord* (in press).
  32. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990;1:466-73.
  33. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait, or intervention. *Am J Epidemiol* 1974;99:325-32.
  34. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. New York: Van Nostrand Reinhold, 1982.
  35. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 1990;322:882-9.
  36. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women: risks within the "normal" weight range. *JAMA* 1995;273:461-5.
  37. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995;122:481-6.
  38. Witteman JC, Willett WC, Stampfer MJ, et al. A prospective study of nutritional factors and hypertension among U.S. women. *Circulation* 1989;80:1320-7.
  39. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr* 1992;55:652-8.
  40. Garrison RJ, Kannel WB. A new approach for estimating healthy body weights. *Int J Obes Relat Metab Disord* 1993;17:417-23.
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