INTRODUCTION

The question of the effect of variations in body weight on longevity is of enormous importance. Due in large part to the industrial and agricultural revolutions, relative body weight has been steadily increasing in the United States and most of the Western world (1). Consequently, rates of obesity have risen dramatically (2). As agricultural and industrial technology spreads into much of the non-Western world, evidence suggests that the relative body weights and rates of obesity are increasing in those populations as well (1). Given this background and the fact that weight is something that is possessed by all humans and therefore of potential interest to all humans, it is not surprising that enormous attention has been focused on relative body weight. Relative body weight is the subject of government policies and guidelines (1), employment policies and guidelines, public education campaigns, insurance policies, a target of the food and pharmaceutical industries, and substantial scientific investigation.

Despite all of this effort and attention, the effect of variations in relative body weight on longevity remains the subject of considerable debate (3–6). At one extreme, some authors suggest that the relationship between relative body weight and longevity is monotonic decreasing (7). In other words, one can never be too thin. At the other extreme, some authors have suggested that relative body weight has little important impact on longevity (8). In the middle, several authors have suggested that the relationship between relative body weight and mortality within a given period of time is U-shaped or J-shaped (9), that the relationships may vary as a function of individuals’ demographic characteristics such as age, sex, and race (10,11), or that the relationships are simply not fully understood at this time (12,13).

We divide this chapter in two broad sections. First, because methodological issues have been and continue to be so prominent in this area, we begin with a review of a few methodological points. We then follow this with a discussion focusing on current findings and needs for future research.

METHODOLOGICAL ISSUES

Beginning in approximately 1987, a number of methodologically oriented reviews have appeared addressing this topic (4,5,14,15). Collectively, these reviews often imply that the effect of relative body weight on mortality depends critically on how the data from prospective cohort studies are analyzed. It has been suggested that the relationship between
relative body weight and mortality within a defined period of time is monotonic increasing (at least above a body mass index of 19 kg/m$^2$) when the following conditions hold: (1) the sample is large; (2) the follow-up is long; (3) subjects dying during the first few years are excluded from the analysis to eliminate the confounding effects of pre-existing disease; (4) smoking is properly controlled for to eliminate its confounding effects; and (5) one does not mistakenly control for variables that are on the causal path from increased relative body weight to mortality (e.g. hypertension, dyslipidemias, glucose intolerance). It is our perception that until recently these statements had been largely accepted as statements of fact.

In addition, though less explicitly advocated, it appears that standard practice has come to favor certain analytic approaches to prospective cohort studies assessing the effect of relative body weight on mortality. Specifically, it appears to have become the standard that: (1) a continuous measure of relative body weight such as body mass index (BMI; kg/m$^2$) is accepted as a valid proxy for the conceptually desired variable of adiposity; (2) a continuous measure of relative body weight such as BMI should be categorized (usually on the basis of quintiles) prior to conducting an analysis; (3) the range of relative body weight associated with minimal mortality is best determined by examining the quintile-defined category in which mortality is at a minimum as opposed to fitting some statistical model to the data and finding the minimum via this model; and (4) individuals with weight fluctuation should be eliminated from the data set.

In this chapter, we question these assumptions. In many cases, these statements and/or practices seem to be based primarily on tradition or assertion. That is, these statements and practices have not been based on mathematical proofs, statistical simulations, or clear empirical demonstrations. In the remainder of this chapter, we critically evaluate these assumptions and practices. We follow this with a discussion of the implications of this work in terms of proposed methodological approaches to the study of relative body weight and mortality, a description of what currently available data seem to show, and finally a speculative discussion on what the currently available data may mean and suggestions for future research.

**Measures of Relative Body Weight as Proxies for Adiposity**

The use of BMI (and other measures of relative body weight) as a measure of relative adiposity has been documented in a number of studies and is generally reported to be highly correlated ($\sim 0.70$–$0.80$) to the percentage of body weight as fat (16). However, an inherent difficulty in using BMI as a proxy for adiposity is that BMI is composed of two components, fat mass (FM) and fat-free mass (FFM). That is: $\text{BMI} = \frac{\text{mass}}{\text{stature}^2} = \frac{(\text{fat mass} + \text{fat-free mass})}{\text{stature}^2} = \frac{\text{fat mass}}{\text{stature}^2} + \frac{\text{fat-free mass}}{\text{stature}^2}$. The index $\text{FM/stature}^2$ has been referred to as the body fat mass index (BFMI) and fat-free mass/stature$^2$ has been used as an indicator of relative FFM (17).

Thus, it may be that the use of BMI as a proxy for adiposity actually masks differential health consequences associated with both FM and FFM.

The rate of mortality associated with BMI is generally higher for lower and higher BMI values and lower for moderate levels of BMI. This curve, generally termed a U-shape curve, may be a function of any number of influences. (The term ‘U-shaped’ is used colloquially and does not imply the symmetry of a perfect U. Rather, it is intended to convey that the relation is convex and non-monotonic with regions at the extremes of the curve in which the mortality rate exceeds the rate at points between those regions.) The most common explanation is that persons with low BMI may suffer from pre-existing diseases that increase their risk for mortality, independent from BMI. Another hypothesis is that BMI, as a reflection of both adiposity and leanness, is not capturing the true relationship between body composition and mortality. Several studies have reported a positive health outcome for increased FFM and negative for increased FM (18). Thus, persons with low BMI may suffer from early mortality not because of BMI per se, but rather because inadequate levels of FFM increase their mortality rate. Stated another way, it may be that the risk of death increases with increasing FM and decreases with increasing FFM.

Recently we explored possible relationships between body composition and mortality using body composition measurements obtained on 1136 healthy subjects. We sought to evaluate the plausible effects of using BMI when FM and FFM had
differential effects on mortality (6). Hypothetical models of mortality were generated (using the real BMI data) in which mortality rate increased monotonically with FM and decreased monotonically with FFM. Using this model we showed that a U-shaped association between BMI and mortality could occur even when: (a) mortality rate increased monotonically with FM; (b) mortality rate decreased monotonically with FFM; and (c) percent body fat increased monotonically (indeed almost linearly) with BMI. Thus, BMI does not necessarily adequately capture the effect of adiposity on mortality rate despite its high correlation with adiposity. Therefore, the need exists for longitudinal studies using precise body composition techniques to study more accurately the relationship between mortality rate and FM and FFM. That is, our analyses suggest that BMI alone may be insufficient to elucidate the relations between body fatness and mortality rate.

There are several studies that are consistent with this hypothesis, but are based on weak body composition measurements. First, although fatness per se and body fat distribution are clearly not synonymous, examining the differential patterns of mortality that have been found as function of fat distribution versus BMI may be illuminating. Folsom et al. (19) followed 41,837 women from the Iowa Women’s Health Study Cohort for 5 years, testing the independent effects of BMI and waist-to-hip circumference ratio (WHR) on mortality rate. Cox regression revealed a U-shaped association between BMI and mortality rate. In contrast, the ‘waist/hip circumference ratio was strongly and positively associated with mortality in a dose-dependent manner’ (p. 483). These conclusions were not substantially changed after controlling for a number of covariates including smoking level, marital status, estrogen use, and alcohol use, such that a 0.15 unit increase in WHR was associated with a 60% greater hazard ratio.

In a small but rigorous study, Keys et al. (20) examined 20-year coronary heart disease (CHD) incidence among 279 middle-aged Minnesota men. Measures were taken of subjects’ BMI, another index of relative body weight (RBW), skinfolds, and body density by under-water weighing at baseline. Twenty-year incidence rates were then evaluated as a function of these variables. It is noteworthy that results tended to be slightly stronger for measures of adiposity than the weight indices. However, due to its very small sample size, this study cannot support firm conclusions.

In a 10-year prospective study in Italy, Menotti et al. (21) examined the association of BMI with mortality rate and skinfold measurements among 8341 men and 1199 women. Among both men and women, results showed a consistent and clear U-shaped association between BMI and mortality. In contrast, the analysis of skinfold data among men showed ‘similar but definitely less clear-cut findings’ (p. 296) and an ‘irregular trend’ after excluding certain subjects. Among women, analyses of skinfold data were less clear and suggested ‘a tendency toward a positive trend with increasing levels of [adiposity]’ (p. 296). Notably, among women, the greatest relative risk (RR) was observed among those with low BMI and high skinfolds, a pattern suggestive of low lean body mass. Unfortunately, BMI and skinfolds were not simultaneously entered into a model to estimate independent effects. A recent analysis by Lee and Jackson (22) also presented mortality data involving measurements of body composition but did not estimate the independent effects of FM and FFM. This is problematic because, given the high correlation between FFM and FM, confounding will occur if each has independent effects on mortality rate and each is evaluated only in separate models.

In summary, very limited data regarding fatness (as opposed to just weight) and its effects on mortality exist. However, those data that do exist suggest the possibility that the elevated risks associated with excessively high BMIs will be seen to be worse when proper body fat rather than body measurements are used.

Categorizing the BMI/Adiposity Measure: Advantages and Disadvantages

The majority of studies of the BMI–mortality relation have transformed the continuously measured variable (BMI) into a polytomous variable. The most common approach seems to be to break the distribution up into five ordered categories with equal numbers of subjects per group based on sample quintiles. There seems to be a perception in some circles that this is the optimal way to analyze the data and, perhaps, even the only way. In con-
trast, we suggest that is certainly not the only way and may not be the best way.

With respect to alternatives, it is well known that survival/mortality outcomes can be modeled as a function of continuous predictor variables through techniques including logistic regression and Cox regression (23). Given that there are alternatives to categorization available, we wish to address some limitations of analyzing the continuous variables as categorical variables and point out a few nuances. The first nuance we wish to address is simply terminological. Many authors refer to the ‘bins’ containing the categories of subjects as the quintiles. For example, they may state that subjects in the fifth quintile are at a relative risk of such-and-such compared to subjects in the first quintile. It should be noted that this is an incorrect use of terminology. There are not five quintiles in a distribution, rather there are four quintiles which cut the distribution into five segments or bins of equal density. The term quintile refers to the cut-points and not the bins created by the cut-points.

Moving beyond terminological trivia, there are some substantive reasons to avoid the use of a categorized measure. First, it is well established that, all other things being equal, categorization can markedly reduce power (24). Second, if the variable being categorized is also being used as a covariate in the analysis, this categorization may result in incomplete control for the variable and therefore residual confounding (25). Third, and perhaps most importantly, the use of a categorized measure can create interpretive difficulties.

Suppose, for example, one investigator studies the relation between BMI and mortality among Pima Indians and another investigator studies the relation between BMI and mortality among Swedes. Because these two groups have such markedly different distributions of BMI, the BMI values represented by subjects with scores above the fifth quintile will be dramatically different in the two studies. If one investigator reports that the RR among subjects in the highest category is much different between the two studies, it is difficult to determine whether this is due to a true difference in the association of BMI with mortality across the two populations or whether this is simply due to the different BMI distributions in the two populations.

Another interpretive difficulty arises when one wishes to make a specific statement about the risk or hazard associated with a given BMI value. Suppose, for example, an investigator wishes to answer the question ‘what is the absolute (or relative) risk of mortality in some defined period of time for an individual with a BMI of 34?’ If a continuous risk function is presented using BMI as a continuous variable, this is a simple question to answer. In contrast, if one only has the absolute risk or RR available for subjects put into various categories, one can only answer questions about the risks for the ‘average’ individual in that category. So, for example, if the only information the investigator has available is the absolute risks or RRs among people with BMI of 32 or greater, then that investigator can say nothing about the risk among individuals with BMI of 32, 34, 36, or any other value. They can only say ‘for the average individual with a BMI of 32 or greater, the risk is…’ One can immediately see the limitation this places on interpreting data in a fine grained way. Among other things, this precludes use of the results of such studies for making predictions about individuals for future research or even in clinical work.

Finally, because the distribution of BMI tends to decrease in density as one moves away from the center of the distribution for virtually every population ever examined, this implies that distributions in the highest and lowest categories are likely to be markedly skewed. This further implies that the means of the ‘bins’ of BMI will be more dispersed than are the medians. This will be especially true in the first and last bins. This will result in the following visual anomaly. If some function of mortality rate (e.g. probabilities of death within some defined period of time) increases linearly with BMI, the plot of that same function of mortality rate as a function of ordinal BMI categories will appear to accelerate. The appearance of acceleration can even occur if the true relation between BMI and the function of mortality is monotonic increasing but decelerating. Thus, the frequently observed graphs in the BMI mortality literature which imply, at least visually, that functions of mortality rate accelerate (i.e. have positive second derivatives) with BMI above a certain level may exaggerate the degree of acceleration. Thus, the use of a categorical BMI measure may create a ‘visual illusion’ that causes us to overestimate the true effect of BMI on mortality.

Given the above, it is our opinion that analyzing mortality as a function of categories of BMI is not optimal and should not be the primary analysis. Some investigators prefer the use of the categorical
data because it allows for marked non-linearity in the association between BMI mortality. However, as has been pointed out elsewhere (26), after an initial exploration with categorized variables, this can be easily accommodated through techniques such as polynomials of BMI.

**Estimating the Range of BMI Associated with Minimal Mortality**

Estimating the point of BMI associated with minimal mortality rate (i.e. the ‘optimal’ BMI) and the range around the point that still represents ‘reasonable’ BMIs for people is a challenging task involving empirical, statistical and conceptual issues. The empirical issue concerns the fact that the BMIs associated with minimal mortality seem to vary with subject characteristics such as age, sex, and race as described elsewhere in this chapter and may also vary as a function of other factors such as genotype. However, beyond the factors of age and sex, knowledge is very limited. Therefore, just as separate standards for BMI ranges associated with greater longevity are sometimes produced for men and women and people of different ages, perhaps the future will bring separate standards for people depending on other factors including ethnicity or genotype. Until greater information is available about genetic modifiers of the BMI–mortality relation, family history may be a useful proxy. For example, the optimal BMI for a person with a strong family history of osteoporosis and no family history of cardiovascular disease (CVD) may be substantially higher than the optimal BMI for a similar person with no family history of osteoporosis and a strong family history of CVD. This remains to be evaluated and is likely to be a fruitful area for future research.

The statistical issues are fairly straightforward. Although the most common approach is again to categorize BMI on the basis of sample quantiles and declare the category with the lowest sample risk or rate as the region of optimal BMI, this may not be an ideal approach. This is because, as stated above, the risk or hazard estimate for each bin is an estimate of the average risk or hazard for people in that bin. Therefore, there is no guarantee that the BMI bin with the lowest risk or hazard contains the BMI point with the lowest risk or hazard. Similarly, it is entirely possible that, if the bins are wide and the curvature of the BMI–mortality curve acute, then the range of the bin may be far greater than the range of BMI associated with reasonably low mortality rate. Of course, the converse is also true.

The alternative is to treat BMI as a continuous variable and estimate the minimum of a polynomial curve fitted to the data. It had been suggested that this would cause a systematic underestimation of the nadir of the curve (27). However, Allison and Faith (28) showed that, though either over- or underestimation could occur, there was no a priori reason to expect a particular bias. Thus, the calculus can be used to determine the BMI associated with minimum mortality rate and confidence intervals can be placed around such estimates using methods described elsewhere (29). In addition, Durazo-Arvizu et al. (30) demonstrated how change-point models can also be used to estimate the BMI associated with minimal mortality rate when the data may not be well characterized by a polynomial.

With respect to the conceptual issues, things are perhaps a bit trickier. Thus far, we have described methods for obtaining a point-estimate of the BMI associated with minimum mortality rate and, possibly, a confidence interval around that estimate. However, of equal importance is developing a range around that point-estimate. Without such a range, one would be left in the absurd position of stating, for example, that the optimal BMI for such-and-such a person is 24.65 and anything above (e.g. 24.7) or below (e.g. 24.6) is not good. So how does one declare such a range? One possibility would be to use the 95% (or other) confidence interval. However, this would conflate statistical precision of estimation with biological ‘tolerability’ of variation in BMI. That is, a wide interval could occur because nature truly tolerates a wide interval of BMIs for the class of individuals under study or because the sample size is small, or both. Conversely, a narrow interval could occur because nature only tolerates a narrow interval of BMIs for the class of individuals under study or because the sample size is large, or both. Alternatively, one might scale the relative risk, odds ratios, or hazard ratios to the average risk, odds, or hazard over the entire sample, find the points where the curve crosses a value of 1.0, and treat those points as the limits of the range. However, this essentially reifies the average and says ‘your hazard of death is OK as long as it’s not above
average'. Who wants to be average when it comes to longevity?

The above methods of determining a range of BMIs associated with minimum mortality rate are flawed because they essentially try to take a judgement that is inherently a subjective value-based judgement and make it objective. Assuming the BMI–mortality curve is convex and differentiable (which seems likely), then the risk is always elevated once one moves off the nadir in either direction. Trying to find points where it is not elevated therefore seems unwise. In contrast, we suggest a simple two-stage approach where the first step is explicitly subjective and the second step involves objective quantification. The first step is to decide how big an increase in risk (either absolute or relative) one is willing to accept. Then, define the limits of the acceptable BMI range as the points on either side of the estimated nadir associated with that degree of elevation.

**Eliminating Early Deaths**

**Rationale**

In prospective studies of the BMI–mortality relationship it has become standard to analyze data without those cohort members who have died early (e.g. within the first 5 years of follow-up) as a means of controlling for confounding from pre-existing diseases. The rationale originates from the observation that many serious illnesses lead to both weight loss and an increased risk of death. Therefore, pre-existing occult disease could confound the BMI–mortality relation and lead spuriously to an apparent increase in the rate of mortality among persons with low BMIs. Thus, many reports have asserted the need to eliminate these confounding deaths by simply disregarding those persons who die early in the follow-up and analyze only those deaths that are less likely to have resulted from pre-existing morbidities. The practice of excluding early deaths in the study of longevity and obesity requires that cohort members who have died in the first 'k years' of follow-up be completely excluded from the data analysis. This technique became standard practice in the absence of analytic proof, Monte Carlo simulations, or even detailed statistical discussions of its properties and effectiveness in reducing confounding due to pre-existing disease.

In order to evaluate the effectiveness of such exclusions we conducted three separate studies using analytic methods, Monte Carlo simulations, and meta-analysis. Our analytic proofs (31) showed that the use of 'k-years exclusion', that is excluding subjects who die during the first k years of follow-up, does not necessarily lead to a reduction in bias in the estimated effect of a risk factor on mortality when this relation is confounded by the presence of occult disease. In fact, it was shown that such exclusion can actually exacerbate the bias in some situations. The analytic studies tell us what can happen but not necessarily what is likely to happen. To provide information on what is likely to happen, we conducted an extensive set of computer simulations (32). These simulations used an actual BMI distribution and overall death rates from large databases representative of the US civilian non-institutionalized population. A hypothetical occult disease was assigned to small proportions of the population and the effects of such occult disease on mortality was set to be strong to exaggerate any effects of excluding early deaths. The results of the simulation were consistent with those of the above analytical study such that removal of persons dying early in the study did not necessarily reduce bias in the estimated BMI–mortality curve due to confounding. In fact, elimination of early deaths usually had little discernable effect on the outcome. Moreover, as the analytic results showed, in some cases elimination of early deaths could even exacerbate the effects of such confounding. While this simulation provides no evidence that the true relationship between BMI and mortality is or is not U-shaped, it does indicate that exclusion of subjects who die early is not as effective as once proposed. Therefore, as stated earlier, it is essential that alternative methods to control for the influence of occult diseases on the relationship between BMI and mortality be explored.

To further examine the effect of k-year exclusions on changes in study outcomes, a meta-analysis was conducted on the effect of early death exclusion on the relationship between BMI and mortality. Studies were selected from a MEDLINE search for the years 1966 to 1996, other meta-analyses, reviews of obesity and mortality, and ancestry analyses. The analysis was conducted on 29 studies with almost 2 million subjects and used a strict set of inclusion criteria for study selection. It was found that the difference in results when early deaths were in-
cluded and excluded was statistically significant, but extremely small and the shape of the curve did not change appreciably. From these results, it was concluded that exclusion of early deaths from the analysis of the BMI–mortality relationship has only a very small and not clinically significant effect (33).

Thus, it is evident from this discussion that the practice of excluding early deaths from analyses of mortality and weight is not statistically sound. The simulation study and meta-analysis both demonstrate that the shape of the mortality risk curve remains U-shaped with or without the exclusion of early deaths. This suggests that either the higher rates of mortality at lower BMIs are not simply artifacts from persons suffering from occult diseases which may precipitate weight loss, or such confounding does exist and early death elimination is incapable of reducing the bias thereby induced. Therefore, more emphasis needs to be placed on acquiring ‘clean’ data rather than on ad hoc statistical fix-ups.

Dealing with Weight Fluctuation

Recently, excluding subjects who have lost more than some minimal amount of weight and/or have had more than some minimal degree of weight fluctuation has become popular (7,34,35). Like excluding early deaths (see above), this practice has been introduced in the absence, to our knowledge, of mathematical proofs, computer simulations, or even detailed statistical discussions of its merits. Though it is beyond the scope of this review to undertake a detailed exploration of this technique, we point out that, like early death exclusion, this elimination of subjects reduces power. Moreover, the degree of weight loss or fluctuation is a continuous variable and it is not necessary to make it categorical and eliminate subjects in one category. Rather, one can simply include the degree of loss or fluctuation in a model as a covariate and also model interactions between it and baseline BMI. Thus, before the practice of eliminating subjects with weight loss or fluctuation becomes de rigueur or is used as a primary analytic approach for BMI mortality studies, proponents of this technique should publish careful analyses of its merits.

RESEARCH FINDINGS

Overall Findings

Having stressed the methodological issues above and their impact on the results of studies, the obvious question is ‘What conclusions can the currently available data support?’ Describing what the currently available data show is relatively simple. When the overall body of literature available is reviewed, the data clearly show that the association between BMI and mortality is U- or J-shaped. Among non-elderly white males and females the nadirs of the curve tend to be around the mid to high 20s. The nadir of the curve can vary substantially as a function of age, sex, race, and possibly other variables. However, the shape of the curve and its nadir does not vary substantially regardless of whether or how one adjusts for smoking, whether or how one adjusts for variables that are likely to be on the causal path from obesity to mortality, and whether or not one eliminates subjects dying during the first few years of analysis or makes other attempts to control for pre-existing disease. Though isolated studies may occasionally show other results, the aforementioned conclusions are those that are clearly supported by the overall body of data (9).

The Effect of Smoking

Smoking is thought typically to be a major confounder of the BMI–mortality relation and to contribute artifactually to the elevated mortality rate at the low end of the BMI continuum. This is hypothesized because smoking strongly increases mortality rate and also has an inverse association with adiposity (4). If this is so, then failure to control for the effects of smoking might help account for the overall J- or U-shaped association typically observed. If it were established that smoking consistently confounds the BMI–mortality association, it would suggest that studies that have not controlled for the effects of smoking would have systematically underestimated the deleterious effect of high BMIs and overestimated the deleterious effect of low BMIs on longevity. Table 3.1 summarizes recent studies that investigated whether smoking confounds the BMI–mortality association. As can be
## Table 3.1 Does smoking confound the BMI–mortality association?

<table>
<thead>
<tr>
<th>Authors</th>
<th>Data source</th>
<th>Sample</th>
<th>Years follow-up</th>
<th>Deaths</th>
<th>Covariates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fontaine et al.</td>
<td>Panel Study of Income Dynamics</td>
<td>1355 American women ≥ 50</td>
<td>4.5 years</td>
<td>110</td>
<td>Age, BMI², smoking, education, 4 health status variables</td>
<td>U-shaped relation with and without smoking in the model</td>
</tr>
<tr>
<td>Sempos et al.</td>
<td>Framingham Heart Study</td>
<td>5209 men and women (28–62 years at baseline)</td>
<td>30 years</td>
<td>&gt; 1900</td>
<td>Age, illness, education, smoking</td>
<td>J-shaped relation; similar BMI at minimum risk of death for smokers and non-smokers</td>
</tr>
<tr>
<td>Brenner et al.</td>
<td>Cohort of German construction workers</td>
<td>7812 men (age 25–64 at baseline)</td>
<td>Mean 4.5 years</td>
<td>167</td>
<td>Age, nationality, alcohol, occupation, smoking</td>
<td>Excess mortality in lowest BMI category reduced but not eliminated by control of smoking</td>
</tr>
<tr>
<td>Dorn et al.</td>
<td>Buffalo Health Study</td>
<td>1308 men and women (age 20–96 at baseline)</td>
<td>29 years</td>
<td>576</td>
<td>Age, education, smoking</td>
<td>U-shaped quadratic relation</td>
</tr>
<tr>
<td>Chyou et al.</td>
<td>Cohort of Japanese-Americans in Hawaii</td>
<td>8006 men (age 45–68 at baseline)</td>
<td>22 years</td>
<td>2667</td>
<td>Age, alcohol consumption, smoking</td>
<td>J-shaped relation</td>
</tr>
<tr>
<td>Seidell et al.</td>
<td>Project of Cardiovascular Diseases</td>
<td>48 287 men and women (age 30–54 at baseline)</td>
<td>Mean 12 years</td>
<td>818</td>
<td>Age, cholesterol, hypertension, diabetes, smoking</td>
<td>In men, excess mortality in lowest BMI category reduced but not eliminated by control of smoking; no relation for women</td>
</tr>
<tr>
<td>Manson et al.</td>
<td>Nurses' Health Study</td>
<td>115 195 women (age 30–55 at baseline)</td>
<td>16 years</td>
<td>4726</td>
<td>Age, contraception, hormone use, family history of myocardial infarction, menopausal status, smoking</td>
<td>Apparent excess risk associated with leanness eliminated when smoking and many other factors were accounted for</td>
</tr>
<tr>
<td>Wienpahl et al.</td>
<td>Members of Kaiser Foundation Health Plan</td>
<td>5184 black men and women (age 40–79 at baseline)</td>
<td>15 years</td>
<td>676</td>
<td>Age, antecedent illness, education, alcohol use, smoking</td>
<td>J-shaped curve for men after controlling for smoking; flat association for women</td>
</tr>
<tr>
<td>Rissanen et al.</td>
<td>Cohort of Finnish men</td>
<td>22 995 (age ≥ 25 years)</td>
<td>Median 12 years</td>
<td></td>
<td>Age, smoking, cholesterol, blood pressure</td>
<td>U-shaped high mortality in lean men 'not entirely attributable to smoking'</td>
</tr>
<tr>
<td>Wannamethee and Shaper</td>
<td>Cohort of British men</td>
<td>7735 (age 40–59 at baseline)</td>
<td>Mean 9 years</td>
<td>660</td>
<td>Age, pre-existing disease, smoking</td>
<td>Increased mortality in lean men seen only in current smokers</td>
</tr>
<tr>
<td>Garrison et al.</td>
<td>Framingham Heart Study</td>
<td>5209 (age 28–62 at baseline)</td>
<td>26 years</td>
<td>679</td>
<td>Age, smoking</td>
<td>BMI–mortality relation in lean subjects confounded by smoking</td>
</tr>
</tbody>
</table>
seen, although at least three studies (7,36,37) suggest that smoking is an important confounder in that the left-most elevation in the J-shaped curve diminished substantially when controlling for smoking (statistically or by restricting the analysis to never smokers), the overwhelming majority of studies have found that the increased mortality among thin subjects (i.e. the J- or U-shaped association) persisted, though often slightly attenuated somewhat, after controlling for smoking.

The minimal power of smoking to account for the excess mortality among thin individuals is further supported by recent comprehensive analyses. In the first, Troiano and colleagues (9) performed a quantitative synthesis of 19 prospective cohort studies and found a U-shaped relation between BMI and mortality regardless of whether or not smoking was controlled for statistically or smokers were eliminated. In a second analysis, The BMI in Diverse Populations Collaborative Group (47) analyzed pooled data from 15 separate epidemiologic studies involving over 200,000 subjects and found that the BMI–mortality association remained essentially unchanged and quadratic (i.e. U-shaped) irrespective of whether or not and how smoking was controlled for or treated in their analyses. Collectively the quantitative syntheses suggest that smoking does not appear to be a major cause of the elevated mortality among the thin.

Nevertheless, when smoking information is available, as it is in most epidemiologic studies, there is no reason not to adjust for it and a possible (though apparently small) benefit in doing so. One question that arises is how one should adjust for smoking. Some investigators prefer to keep the entire data set intact and statistically adjust for smoking. Others seem to believe that the only valid approach is to eliminate any subject who has ever smoked from the data set. The answer to this questions sees to depend, in part, on what one is prepared to believe and see as paramount in the BMI–smoking–mortality relationship. Two non-exhaustive possibilities seem to predominate current thinking: (1) Smoking confounds the BMI–mortality relation, smoking is poorly measured in epidemiologic studies, people can accurately report if they have ever smoked, and the true causal relation (not the observed association) between BMI and mortality rate is unaffected by smoking status; and (2) the true causal relation (not the observed association) between BMI and mortality rate may be affected by smoking status and measurements of smoking status in epidemiologic studies perfectly capture all of the variance in exposure to any of the deleterious aspects of smoking (e.g. tar exposure). If the first possibility were true, then any attempt to control for smoking statistically would fail as a result of measurement error induced residual confounding (25), whereas studies of never-smokers only would yield unbiased estimates of the effects of BMI on mortality for both never-smokers and ever-smokers. In contrast, were the second possibility true, then statistical adjustment will fully control for any confounding by smoking and including all subjects in the analysis will provide the best estimate of the average effect of BMI on mortality rate across the whole population of smokers and non-smokers. Of course, in this second case, one would probably wish to estimate effects of BMI on mortality rate that varied as a function of smoking status and this could be accomplished by use of interaction terms (23). In reality, neither of the two possibilities listed above is likely to be strictly true and the best approach may be to fit the model involving interactions with smoking status where a category is explicitly coded for never-smokers. This allows simultaneous estimation of the effects among never-smokers and among smokers. Both can then be viewed and readers can determine for themselves what the most plausible estimate is for the overall population and different smoking subgroups.

Aging and the Elderly

A number of studies have investigated whether age modifies the relation between body weight and mortality. Certainly several studies of BMI and mortality among older adults have reported weak effects of obesity on mortality rate and/or very high nadirs for the BMI–mortality curves (38,41,48–50). The Build Study (51) found that the relation between BMI and mortality was U-shaped, and that the BMI associated with minimal mortality increased with age. In a Norwegian study (27), plots of the log of the mortality rate against BMI categories also revealed a U-shaped association. Although it was less clear whether the BMI associated with minimal mortality increased with age, the overall
curves did flatten substantially with age. However, it should be noted that Waaler (27) did not control for the effects of smoking.

More recent studies that examined the effect of age on the BMI–mortality association have controlled for smoking. In a Finnish cohort of 17000 women followed for 12 years, there was a U-shaped BMI–all-cause mortality relation among non-smokers 25 to 64 years of age. Among women aged 65 or greater, mortality varied little according to BMI (52). Among white women from the Seventh Day Adventist cohort who never smoked, the RR of death associated with elevated BMI was lower among 55- to 74-year-olds than for 30- to 54-year-olds. For these older women, the minimal mortality was in the group with BMIs from 23 to 24.8 (53). Although the nadirs of the curves were much higher, a recent study by Seccareccia et al. (54) of over 60 000 Italian subjects again shows the increase in the nadir with age.

In one of the largest studies, Stevens et al. (34) investigated mortality over 12 years as a function of BMI across six age groups (30–44, 45–54, 55–64, 65–74, 75–84, and ≥ 85) among 324135 never-smokers with no apparent pre-existing disease from the American Cancer Society’s Cancer Prevention Study I. Results indicated that, although greater BMI was associated with higher all-cause and CVD mortality, the RR associated with greater BMI declined somewhat with age (e.g. for men the RR of CVD mortality with an increment of 1.0 BMI units was 1.10 for 30–44-year-olds and 1.03 for 65–74-year-olds).

Bender and colleagues (55) recently examined the effect of age on excess mortality associated with obesity among 6193 obese persons enrolled in the Duseldorf Obesity Mortality Study (DOMS). When grouped into four groups based on approximate quartiles of age and BMI, it was found that the overall risk of death increased with increased body weight, but that obesity-related excess mortality declined with age at all levels of BMI.

On the whole, these studies suggest that the relative increase in rate of death associated with increased BMI is somewhat lower for older adults than for younger adults and the BMI associated with minimum mortality rate increases with age. However, as Stevens et al. (56) point out, the absolute increase in rate of death can be higher in an older than younger person even when the relative increase is lower.

**Ethnicity**

The majority of research on the effects of body weight, body composition and longevity has been conducted on samples of European Americans (57). While it is clear that obesity in African Americans, most notably women, is associated with a number of risk factors (58,59), the relation between obesity and mortality/longevity among African Americans is not as clear as it is in white individuals.

On the basis of a 14-year mortality study with X-ray-determined adiposity, Comstock et al. (60) concluded that the excess mortality of overweight/obese persons was more marked for European Americans than for African Americans. By the same token, in a cohort of 2731 African American women members of the Kaiser Foundation Health Plan who were followed for 15 years, Wienpahl et al. (44) found an essentially flat BMI–mortality association across the entire range of BMI. However, although the U-shaped relation between BMI and all-cause mortality was not significant, Stevens et al. (61) found that, among African American men, obesity was associated with increased risk of mortality from ischemic heart disease (IHD). More recently, Stevens et al. (11) examined the association of BMI to all-cause and CVD mortality among 100 000 White and 8142 African American women from the American Cancer Society Prevention Study I. At the 12-year follow-up, they found a significant interaction between ethnicity and BMI for both all-cause and CVD mortality. That is, among white women BMI was associated with all-cause mortality in all four groups (defined by smoking status and educational attainment). In African American women with less than a high school education there was no significant association between BMI and all-cause mortality. However, there was a significant association among high school-educated African American women. Models using the lowest BMI as the reference group among never smoking women with at least a high school education indicated a 40% higher risk of all-cause mortality at a BMI of 35.9 in the African American women versus 27.3 in the white women. Stevens et al. concluded that, although educational attainment modifies the impact of BMI on mortality, BMI was a less potent risk factor in the African American women than in the white women.

Similar results have been obtained by others (35,62–65). That is, the bulk of the studies conduc-
ted suggest that the effect of given BMI increase on mortality rate may be less deleterious among African Americans. Two more recent studies have emerged with relatively large and high quality samples of African Americans (66,67). These studies show that there clearly is a deleterious effect of obesity on mortality rate among African Americans, though the BMIs associated with minimum mortality rate may be slightly higher among African Americans.

With regard to the BMI–mortality association among persons of other ethnic origins, the data are relatively sparse. In a sample of Micronesian Nauruans and Melanesian and Indian Fijians, obesity was not significantly associated with an elevated mortality rate (68). Among a sample of 8006 Japanese American men living in Hawaii who were followed for 22 years, a significant quadratic (J-shaped) relation was found between BMI and mortality independent of the effects of smoking and alcohol consumption (42). Similarly, among a cohort of over 2000 Japanese adults over age 40, there was a U-shaped relation between BMI and mortality rate with a nadir in the range of 23–25. However, among a cohort of 2546 East Indian and Melanesian Fijians followed for 11 years, the association of BMI to all-cause and CVD mortality was generally inconsistent (69). Despite the known associations between body weight and diabetes and other obesity-related diseases found among Mexican Americans, data have revealed lower than expected rates of mortality, based on known body weights (70). To date, the data available on the BMI–mortality association among other ethnic groups (e.g. Native Americans, Alaska Natives) are limited. Hanson et al. (71) found that, among a cohort of 814 diabetic and 1814 non-diabetic Pima Indians, a U-shaped relationship between BMI and mortality was found in men, but not women. It was reported that excess mortality among lighter individuals was present in those persons who were gaining weight. Thus, they concluded that pre-existing illness may only partially explain the high mortality among lighter persons.

**Could the Elevated Mortality Rate Among the Thin Be Causal?**

As we have pointed out, most studies find that thin people (e.g. 18 < BMI < 24) tend to have higher mortality rates than more ‘mid-BMI’ people (e.g. 24 < BMI < 28). There are several non-exclusive possible explanations for this. The most commonly mentioned is that this is due to confounding by smoking or pre-existing disease. A second is that this has to do with using BMI as a proxy for adiposity. These two possibilities were discussed elsewhere in this chapter. A possibility that seems to receive less consideration is that being in the mid-BMI range may cause one to be at lower risk of death from certain causes. Consider a few examples that range from well-supported to plausible-but-highly-speculative. It is clear that relative to thinness, being in the mid-BMI range is protective against osteoporosis (72,73). There is a clear biological mechanism because thinness is a clear risk factor for hip fracture (74) which is in turn a risk for mortality (72,75). Thus, it is plausible that thinness (at least among the elderly) causes increased mortality rate through an osteoporosis/fracture pathway.

Though more speculative, it is possible that, relative to being in the mid-BMI range, people in the thin range are more potently affected by or more susceptible to certain forms of infection and injury. Finally, given that most modern Americans (as well as the members of many other countries) have inadequate intake of fruit, vegetables, fiber, and many micronutrients (76,77), it may be that thin people, simply by virtue of eating less total food, are at increased risk of nutrient deficiencies despite adequate caloric intake. That is, just as laboratory animals live longer when calorically restricted only when one insures adequate micronutrient intakes (78,79), thinness in humans may be deleterious only because it is, among many people, associated with inadequate intake of certain nutrients.

Though many of the potential explanations above are speculative, they are plausible. We believe the possibility that thinness causes increased mortality rate deserves to be taken seriously and that further research to understand rather than dismiss the observed elevated mortality rate among the thin is warranted.

**Putting the Results in Perspective**

Statements about RRs, hazard ratios, and odds ratios are interpretable to many scientists but often do not have an intuitive appeal to clinicians, policy
makers, and the lay public. Therefore, it is useful to consider the effect of varying levels of BMI on mortality rate with different metrics. Two metrics that may be useful are the number of annual deaths due to obesity and the years of life an individual can expect to lose from being a given degree above the optimal BMI. The former may be especially useful for policy makers whereas the latter may be more useful for clinicians and individual patients.

**Attributable Deaths**

At a societal level, one can estimate the number of deaths each year that are attributable to obesity and overweight. Recently, Allison *et al.* (32) estimated that of adults who were alive in the United States at the beginning of 1991, somewhere between 280,000 and 325,000 fewer would have died during that year, if they had never been overweight or obese. More than 80% of these deaths occurred among individuals with BMIs over 30.

**Estimated Years of Life Lost**

The individual patient may be less concerned with numbers for the whole population than with answers to questions like ‘How many years less am I expected to live given that my BMI is such-and-such?’ This question calls for an analysis of years of life lost (YLL). Stevens *et al.* (56) recently published such an analysis. However, they restricted this analysis to a 12-year period rather than estimating YLL across the remaining life. We believe that this will markedly underestimate YLL and is likely to create spurious positive correlations between baseline age and YLL. Therefore, we believe additional studies estimating YLL across the entire life are necessary to provide meaningful values in this metric.

**Change in Weight**

Dramatic effects of obesity on mortality rate have been demonstrated in studies of laboratory rodents (80). When obese animals are compared to non-obese, the lean outlive the obese regardless of the type of obesity (e.g. polygenic factors or dietary induction). These findings are buttressed by the life-prolonging effects shown to be achieved by caloric restriction (CR). CR should not be conflicted with lower body weight or lower body fat. However, CR clearly results in lower body weight and is the most common method by which humans achieve lower body weight. Therefore, it is worth noting that CR achieved by various means and resulting weight loss has been demonstrated to result in increased longevity in a variety of animal species, such as spiders, water fleas, fish, and laboratory rodents (81).

Obesity (at least when severe) is clearly associated with an increased mortality rate. Moreover, weight loss is clearly associated with reductions in many risk factors. Therefore, one might wish to conclude that weight loss among the obese will increase lifespan. However, to date, data to support this conjecture are sparse at best. Indeed, after a review 13 papers from 11 samples of adults in the United States and Europe, Andres *et al.* (10) wrote:

Despite the diversity of the populations studied, the degree of ‘clinical clean-up’ at entry, the techniques used to assess weight change, and the differences in analytic techniques (including consideration of potentially confounding variables), certain conclusions may be drawn. Evidence suggests that the highest mortality rates occur in adults who either have lost weight or have gained excessive weight. The lowest mortality rates are generally associated with modest weight gain. (p. 737).

However, the puzzling finding that weight loss is predictive of increased mortality rate is still subject to considerable inquiry. In an insightful review of the literature, Williamson (82) noted that analyses should be restricted to those for whom weight loss is generally recommended, i.e. obese individuals. Furthermore, as in the study of BMI per se, in the study of the effects of changes in BMI the possibility of confounding by occult disease remains a substantial issue. This is illustrated by Williamson (82) who show that unintentional weight loss is at least as common as is intentional weight loss. Williamson describes a study (83) of intentional weight loss among 203 adults with recent myocardial infarction who had been instructed to lose weight. The results of this study indicated that subjects losing at least 5 kg had a 54% lower mortality rate during the subsequent year. In an observational study, Lean *et al.* (84) found that weight loss was associated with greater longevity among identified and treated diabetics. These results suggest possible benefits to weight loss among obese individuals suffering from comorbidities.

Recently, a series of large epidemiological studies
Table 3.2  Two by two table weight loss by intention

<table>
<thead>
<tr>
<th></th>
<th>No intention to lose weight</th>
<th>Intention to lose weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not lose weight</td>
<td>0.187</td>
<td>0.414</td>
</tr>
<tr>
<td>Lost weight</td>
<td>0.045</td>
<td>0.354</td>
</tr>
</tbody>
</table>

Based on Meltzer and Everhart (88).

have been conducted to address this issue. Williamson and colleagues observed that when analyses are restricted to weight loss among never-smoking, overweight individuals who reported that their weight loss was intentional, weight loss was associated with either a beneficial effect or no effect. For further discussion of these studies, see French et al. (85), Kuller (86), and Williamson et al. (87).

However, it is important to realize that the so-called intentional weight loss studied by these investigators may often be unintentional. Consider the following. Meltzer and Everhart (88) studied participant attributions of weight loss intention in a large population-based survey. Among women, they found the following:

- 76.8% of overweight women reported attempting to lose weight.
- Of those women attempting to lose weight, 46.1% did lose weight.
- The adjusted odds ratio for weight loss given that one intends to lose weight is reported to be 3.52.

Similar results were obtained for men. Using these three numbers and some algebra, one can derive the $2 \times 2$ table shown in Table 3.2 expressed in proportions. Applying the standard attributable risk approach, this implies that 46% of overweight women who intend to lose weight do lose weight, but that 19% would have lost weight even if they had not intended to do so. Therefore, the fraction of weight loss among overweight women who intend to lose weight that is due to factors other than their intention is about 41% (i.e. 19/46). These calculations suggest that some large sub-portion of those who have been designated as intentional weight losers in past studies may have actually lost weight through some other mechanism such as occult illness. If this were true, the currently observed equivocally beneficial effects of what we currently label intentional weight loss may markedly underestimate true benefits due to residual confounding by occult disease. This points out the severe limitations of observational (non-experimental) studies in this area.

Moreover, perhaps we are misguided by focusing on ‘intentionality’ at all. In many of the observational studies of so-called intentional weight loss, subjects were initially measured decades ago (82, 87). By what methods did they achieve weight loss decades ago? Among others, by drugs and surgical procedures that are far less safe than those currently available. Even as late as 1997 some widely prescribed drugs were removed from the market because of dangerous effects (89). Still today, methods for intentionally inducing weight loss include fad diets (90), herbal supplements of untested safety, bulimia and other methods of highly questionable safety. Hence, it appears ill advised to estimate the effects weight loss achieved by medically recommended methods by studying weight loss that is merely reported to be ‘intentional.’ What is needed is studies of weight loss that is produced among obese humans by modern methods that are accepted by mainstream medicine.

Presently, a well-controlled non-randomized study of weight loss produced by surgery among morbidly obese adults is underway (91). Mortality results are not yet available. A randomized clinical trial (RCT) testing whether producing weight loss through medically accepted methods among obese people can reduce mortality rate could settle these issues (92). Presently, the National Institute of Diabetes, Digestive and Kidney Diseases is designing a large multi-center study termed SHOW. Although this RCT will examine mortality as a secondary outcome, it is not necessarily powered to detect differences in mortality rates.

Our perspective of the admittedly incomplete evidence regarding the effect of weight loss on mortality rate is portrayed in Figure 3.1—an iconic representation of the currently available literature and a conjecture of what the future might bring. This figure is intended to convey that as studies of weight loss and mortality rate have become methodologically more sound, what initially appeared to be a harmful effect has progressively shifted to be neutral.
Figure 3.1 Iconic presentation of the estimated effects of weight loss (WL) on mortality with varying study designs

at worst and possibly even somewhat positive. When studies of weight loss that is intentionally induced among obese individuals through accepted medical interventions are included, it is plausible to conjecture that the effect may become strongly positive. Still, there is a great gap between conjecture and demonstration and we must continue to look for stronger studies that can provide this demonstration (or lack thereof).

Change in Body Composition

Finally, as discussed above, studies of body composition at a single point in time, as opposed to just body weight at a single point in time, may tell different stories. The same may hold true for studies of change in body composition versus change in weight. To examine this possibility, Allison et al. (32) analyzed mortality rate in two epidemiologic studies, the Tecumseh Community Health Study and the Framingham Heart Study. In both, change in weight and fat (via skinfolds) across two points in time were available. In both studies, weight loss and fat loss were, respectively, associated with an elevated and reduced mortality rate. Each standard deviation (SD) of weight loss (approximately 5.5 kg across both studies) was estimated to increase the hazard of mortality by about 35%. In contrast, each SD of fat loss (10.0 mm in Tecumseh and 4.8 mm in Framingham) reduced the hazard of mortality by about 16%. Thus, among individuals that are not severely obese, weight loss (conditional upon fat loss) is associated with increased mortality rate and fat loss (conditional upon weight loss) with decreased mortality rate. These results, if confirmed in future studies, have important implications for clinical and public health recommendations regarding weight loss. They suggest that weight loss should only be recommended under conditions where a sufficient proportion of the weight lost can be expected to be fat. Unfortunately, what those conditions are and what the minimum proportion is remains unknown at his time.

DISCUSSION

In this discussion section, we begin by reiterating key methodological conclusions. We follow this with a discussion of what we believe the currently available data on relative body weight and mortality show and what the currently available data on body weight and mortality mean. We can point out that these are not necessarily the same thing.

Based on the information reviewed above, we reach the following conclusions:

1. While controlling for smoking either by stratification or statistical adjustment is a sound process and smoking is a plausible confounder of the BMI–mortality relationship, in actual data sets, adjusting for smoking has very little impact on the results of the analysis. This does not imply that one should not control for smoking. It only implies that smoking appears to be an unlikely explanation for the U- and J-shaped relationships frequently observed between BMI and mortality.

2. Excluding subjects who die during the first few years of follow-up is not a reliable way of controlling for confounding due to occult disease. In the presence of confounding due to occult disease such exclusions can either increase or decrease the bias, although in practice such exclusions appear to make little difference. Because such exclusions can actually increase the bias under some circumstances and result in an overall reduction of sample size, we do not recommend that subjects dying during the first few years be excluded from the analyses.

3. There is no a priori reason to assume, if a quadratic model is fitted to describe the relationship between BMI and mortality and the minimum of this quadratic equation solved for the resulting estimated BMI associated with minimum mortality, that the estimate will systematically overestimate the true BMI associated with minimum mortality. However, other methods for es-
timating the BMI associated with minimum mortality are available and may be superior. These methods do not require that BMI be categorized into quantiles but can be applied to BMI treated as a continuous variable.

4. BMI is a continuous variable and, as with other continuous variables, there is little advantage to categorizing BMI in the final analysis. It is certainly useful to treat BMI categorically in an exploratory manner. However, it is possible to treat BMI continuously in the final analysis and there are a number of advantages to doing so.

5. Though highly correlated with body fatness, BMI is not a true measure of body fatness and it cannot be assumed that BMI will have the same relationship with mortality in either direction or form as will a valid measure of body composition. Therefore, it is strongly suggested that future research consider including measures of body composition rather than just BMI.

6. There is substantial variation in results from study to study, some of which is probably due solely to random sampling variations. Because of this, selective review of the data can be used to support virtually any conclusion. Therefore, it is essential that reviews of the literature, if they are intended to be objective, evaluate the entire body of the literature to the greatest extent possible. This approach is exemplified in the recent papers by Allison et al. (32), Troiano et al. (9), and The BMI in Diverse Populations Collaborative Group (47).

7. The relationship between BMI and mortality appears to vary substantially by age, sex, and race. Other variables yet to be fully explored may also moderate this relationship. Therefore, it is ill advised to generalize from studies in the one population (e.g. white middle-aged females) to other populations (e.g. young black males or elderly Asian females). Moreover, investigators who wish to make broad statements about the overall ‘average’ relationship between BMI and mortality for the US population will need to rely on samples that are representative of the US population. Finally, this implies that it is wise for investigators to attempt to stratify by or fit interaction terms with their demographic variables and other possible moderators when analyzing the relationship between BMI and mortality.

What the Available Data Show

The above conclusions can be used to guide future research investigating the effect of variations in relative body weight on longevity. Collectively, they suggest that measures of body composition should be used over measures of body weight whenever possible, that subjects dying during the first several years not be excluded from the analysis, that measures of either body composition or relative body weight can be treated as continuous variables, that statistical methods can be used to estimate the BMI (or degree of adiposity) associated with minimum mortality, and, finally, that alternative methods be pursued to reduce the possibility of confounding due to occult disease (e.g. more careful clinical evaluation at baseline).

However, what the data show and what the data mean are not necessarily the same thing. Because the association between BMI and mortality is U-shaped does not mean that the causal relationship between BMI and mortality is U-shaped. As we have shown, the fact that relationship persists even after eliminating subjects who die during the first several years of follow-up cannot be taken as evidence that this relationship is not due to confounding for pre-existing disease. Moreover, as we have shown, the fact that the relationship between BMI and mortality maybe U-shaped does not necessarily imply that the relationship between adiposity and mortality is U-shaped. Thus, it is difficult to know exactly what to conclude from the currently available data. Certainly, the currently available data do demonstrate that unusually high levels of BMI (e.g. BMIs greater than the high 20s) are associated with increased mortality and this is entirely consistent with a great deal of clinical and basic laboratory research. However, over the range of BMI from about 28 down, the picture is not clear. The human epidemiological data suggest that lower BMIs are associated with increased mortality and this is entirely consistent with the results of animal work which show that caloric restriction is capable of producing substantial increases in longevity (81). Finally, such work is not consistent with the clinical evidence that suggests that intentional weight loss is almost always associated with a reduction in morbidities even among
those who are only mildly overweight (93).

It appears that, to date, the approaches that investigators have taken for evaluating the association between variations in relative body adiposity and mortality have been to rely on weak epidemiologic data. By ‘weak’ we mean data in which the measured independent variable (e.g. BMI) is only a proxy for the conceptual independent variable (i.e. adiposity) and the most plausible confounding factor (i.e. occult disease) is not measured but only inferred. In the face of such weak data, the approach that some authors seem to believe will yield valid conclusions is a strong statistical analysis. In our opinion, this is an example of what has been called ‘under-design and over-analysis’. Though we are as appreciative of the power and beauty of good statistical models as anyone, we believe that no amount of statistical analysis will make weak data strong. If stronger conclusions are to be drawn from future studies we believe that stronger measurements and designs will have to be employed. Such designs should clearly include measures of adiposity, detailed and thorough clinical evaluations of health status at study onset, and possibly even the use of large-scale randomized trials (92).

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