Hypothesis Concerning the U-shaped Relation between Body Mass Index and Mortality

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Numerous studies have documented a U- or J-shaped association between body mass index (BMI) (kg/m²) and mortality, such that increased mortality rate is associated with relatively low and high BMI values. It has been argued elsewhere that the elevated mortality rate observed at lower BMI values actually results from the effects of unmeasured confounding variables, in particular smoking status and preexisting disease. In this paper, the authors present an additional explanation for the phenomenon, i.e., nonspecific measurement. They propose that differential health consequences of fat mass and fat-free mass can be masked by the use of BMI when studied in relation to mortality. To illustrate this point, they use body composition data from 1,137 healthy adults and specify a hypothetical underlying BMI-mortality model in which the logit of death increased linearly with fat mass and decreased linearly with fat-free mass, and % fat increased monotonically with BMI. The results indicate that, even under these specifications, the authors can recover a U-shaped association between BMI and mortality. Consistent with previous suggestions in the literature, future epidemiologic studies that examine the association between adiposity and mortality should prioritize the use of body composition measures. Am J Epidemiol 1997;146:339-49.

body composition; body mass index; confounding factors (epidemiology); mortality; obesity; occult disease

The relation between body mass index (BMI) (kg/m²) and longevity remains an area of interest, importance, and controversy (1−8). One of the main points of controversy concerns the elevation in mortality risk at the low end of the BMI continuum. That is, the majority of studies observe a U- or J-shaped relation between BMI and the risk of mortality within a defined period of time (e.g., references 9−15). In other words, subjects with the highest and lowest relative weights die earlier than subjects with more intermediate levels of relative weight. The robustness of this association is most strongly suggested by Troiano et al. (16) in their comprehensive meta-analysis of the BMI-mortality association. Among a multinational sample of studies, these investigators found clear evidence of a U- or J-shaped relation.

The increased risk of mortality at the low end of the continuum seems quite counterintuitive to many investigators (2, 3). It is inconsistent with the generally monotonic relation between BMI and indicators of morbidity (17), including diabetes mellitus, hypertension, stroke, dyslipidemia, and cardiovascular disease among others (18−20). Moreover, it stands in contrast to the fairly consistent observation that weight loss reduces risk factors for a variety of illnesses (21−24).

In response to this counterintuitive finding, several authors have suggested that the elevated risk of mortality at the low end of the BMI continuum is an artifact due to confounding. The two confounding variables most frequently cited are smoking and preexisting “occult” disease (25, 26). In regard to occult disease, several studies suggest that elimination of subjects who die during the first several years of follow-up results in a dampening of the left tail of the BMI-mortality curve (27−29). For example, in an analysis of the Nurses’ Health Study, Manson et al. (27) suggested that excluding subjects who died during the first 4 years of follow-up had such an effect on 16-year mortality. The authors concluded that “the apparent excess risks of leanness were found to be artifactual and were eliminated after we accounted for . . . subclinical disease” (27, p. 683).

On the other hand, the majority of studies which attempt to control for these potentially confounding variables continue to show the U-shaped relation previously described (4−6, 30−33). In fact, the meta-
analysis by Troiano et al. (16) yielded comparable findings, which led the authors to conclude, “Failure to exclude persons with disease was not associated with a rise in mortality at low BMI with either short or long follow-up. Moreover, the increased mortality observed in the lowest BMI groups could not be fully explained by pre-existing illness . . . because the relationship was still present after controlling for these factors. . .” (16, p. 71). Similarly, the investigation by Waaler (13) of over 1 million Norwegians found no significant effect of early death exclusion specifically on the left tail of the BMI-mortality curve. Waaler concluded, “The hypothesis that the U-shape is a product of already existing fatal diseases can therefore be dismissed” (13, p. 22). Thus, whether or not the presence of occult disease causes the elevated mortality seen among individuals with the lowest BMIs remains open to question and an area for further research.

In this paper, we suggest an additional possible explanation for the elevated mortality risk at the low end of the BMI continuum. Specifically, we conjecture that this elevation may be due to a measurement problem, i.e., the use of BMI as a measure of “adiposity” may create an artifactual relation. We suggest that, while other factors may also underlie the observed U-or J-shaped association between BMI and mortality, the measurement issue described herein may itself be an important factor that deserves greater attention.

To begin, it is well known that BMI is highly correlated and monotonically associated with % body fat (34, 35). However, consider the following re-expression:

\[ \text{BMI} = \frac{\text{mass}}{\text{stature}^2} = \frac{\text{fat mass} + \text{fat-free mass}}{\text{stature}^2} = \frac{\text{fat mass}}{\text{stature}^2} + \frac{\text{fat-free mass}}{\text{stature}^2}. \]

Expressed in this manner, it is obvious that BMI includes (at least) two distinct components, fat mass (FM) and fat-free mass (FFM), relative to stature. The index (FM)/stature^2 has been suggested as a measure of adiposity and referred to as the body fat mass index (BFMI) (36). Similarly, the use of (FFM)/stature^2 has been suggested as an indicator of relative fat-free mass (36).

It is generally thought that increasing amounts of FM pose a threat to health and longevity (7). Conversely, it may well be that, all other things being equal, increasing amounts of FFM enhance health and longevity (37). Indeed, past research has suggested that body composition rather than body mass is a major determinant of cardiovascular disease risk factors (18, 38–40).

Given the above, it is possible that the logit of the probability of death within some finite period of time could be expressed with the following model:

\[ \text{Logit}(\pi) = \beta_0 + \frac{\text{FM}}{m^2} + \frac{\text{FFM}}{m^2}, \]

where \( \text{Logit}(\cdot) = \log(\cdot/(1 - \cdot)) \), \( \pi = P(D = 1|\text{FM}, \text{FFM}) \), \( D = 1 \) if “dead,” and \( D = 0 \) otherwise. The coefficients are restricted as follows: \( \beta_1 > 0 \) and \( \beta_2 < 0 \). This reflects a positive effect of FM and a negative effect of FFM on mortality. Data published by Keys (41) further support the assignment of positive and negative signs to \( \beta_1 \) and \( \beta_2 \), respectively. Investigating all-cause mortality at 35-year follow-up in the Twin Cities Prospective Study, Keys found a positive association between “body density” and mortality (controlling for other fitness indexes), but a negative association between BMI and mortality.

Were this the true model underlying risk of death, then the risk of death at any BMI relative to some standard would be a composite of the relative difference in FM and FFM at that BMI level compared to the standard BMI level. Under these circumstances, it is possible that the risk of mortality within a defined period of time can be non-monotonic over the range of BMI even when the following conditions are met:

1. The logit of death increases linearly with increasing FM.
2. The logit of death decreases linearly with increasing FFM.
3. Percent fat increases monotonically with BMI.

We illustrate this point with a hypothetical example.

**EXAMPLE**

**Sample**

For this example, measurements of height, weight, FM, and FFM on individual subjects were originally pooled from several data sets of apparently healthy adults. The data are retrieved from several references (42–48). Subjects with BMIs <16 or >40 were then excluded from this pooled sample for the present study. The resulting pooled sample (with extreme BMI excluded) includes 1,137 apparently healthy adults aged between 18 and 65 years. Detailed descriptive statistics for this pooled sample are described in table 1. In this table, the method of the body composition measurement used in each source of the data sets is also included. Correlations between measurements are described in table 2.

The primary source of data from Kotler et al. (42) consists of a group of 1,083 healthy volunteers (31 percent white, 69 percent black), which alone consti-
TABLE 1. Descriptive statistics for the measurements in the example sample with extreme body mass index (BMI) excluded

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kotler et al. (42)</th>
<th>Hoovar et al. (43)</th>
<th>Kreitzman et al. (41)</th>
<th>Racette et al. (45)</th>
<th>Ravussin et al. (46)</th>
<th>Sjödin et al. (47)</th>
<th>Veltl et al. (48)</th>
<th>Total (pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD*)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>41.9 (10.7)</td>
<td>54.5 (2.4)</td>
<td>47.3 (7.5)</td>
<td>39.7 (5.9)</td>
<td>28.0 (4.1)</td>
<td>25.5 (1.9)</td>
<td>21.1 (1.5)</td>
<td>41.6 (10.9)</td>
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<td></td>
<td>18-65†</td>
<td>52-58</td>
<td>31.5-60.3</td>
<td>24-46</td>
<td>20.5-32.0</td>
<td>23-28</td>
<td>19-23</td>
<td>18-65</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>67.4 (13.7)</td>
<td>58.9 (5.3)</td>
<td>87.4 (12.2)</td>
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<td>79.7 (14.8)</td>
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<td>42.5-64.4</td>
<td>79.6-110</td>
<td>61.4-102</td>
<td>48.2-81.5</td>
<td>51.4-66.9</td>
<td>38.0-115</td>
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</tr>
<tr>
<td></td>
<td>166.9 (8.4)</td>
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<td>168.4 (6.9)</td>
<td>163.9 (6.4)</td>
<td>175.1 (5.9)</td>
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<td>152-172</td>
<td>155-180</td>
<td>155-174</td>
<td>166-181</td>
<td>164-188</td>
<td>161-178</td>
<td>125-200</td>
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<td>BMI</td>
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<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>24.1 (4.2)</td>
<td>22.0 (2.5)</td>
<td>30.9 (4.5)</td>
<td>34.0 (2.9)</td>
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<td>FM* (kg)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>17.2 (9.8)</td>
<td>15.8 (5.5)</td>
<td>33.1 (10.7)</td>
<td>41.0 (6.6)</td>
<td>16.7 (10.1)</td>
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<td>17.5 (10.2)</td>
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<td>10.9-24.4</td>
<td>14.7-51.6</td>
<td>34.1-55.2</td>
<td>4.3-31.6</td>
<td>6.2-11.0</td>
<td>0.38-20.4</td>
<td>0.38-62.3</td>
</tr>
<tr>
<td>FFM* (kg)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>50.2 (10.5)</td>
<td>43.1 (1.9)</td>
<td>54.2 (4.4)</td>
<td>50.2 (4.9)</td>
<td>63.0 (6.4)</td>
<td>55.7 (12.0)</td>
<td>50.7 (7.7)</td>
<td>50.3 (10.4)</td>
</tr>
<tr>
<td></td>
<td>26.9-84.0</td>
<td>41.5-46.0</td>
<td>49.6-63.6</td>
<td>41.1-56.4</td>
<td>53.4-70.2</td>
<td>42.0-72.3</td>
<td>36.2-60.0</td>
<td>26.9-84.0</td>
</tr>
<tr>
<td>% Fat</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>24.7 (11.1)</td>
<td>26.3 (6.8)</td>
<td>37.1 (7.6)</td>
<td>44.8 (4.3)</td>
<td>19.7 (9.0)</td>
<td>14.4 (3.7)</td>
<td>16.5 (11.3)</td>
<td>24.9 (11.3)</td>
</tr>
<tr>
<td></td>
<td>2.1-55.1</td>
<td>19.0-37.0</td>
<td>22.9-50.0</td>
<td>38.6-53.4</td>
<td>7.0-31.0</td>
<td>10.9-19.0</td>
<td>0.74-36.1</td>
<td>0.74-55.1</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>1,083</td>
<td>6</td>
<td>11</td>
<td>14</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>1,137</td>
</tr>
<tr>
<td>Method used for body composition measurements</td>
<td>Bio-impedance</td>
<td>Dual energy x-ray absorptiometry</td>
<td>In vitro neutron activation analysis</td>
<td>Bio-impedance</td>
<td>Densitometry</td>
<td>Isotope dilution</td>
<td>Densitometry</td>
<td></td>
</tr>
</tbody>
</table>

* SD, standard deviation; FM, fat mass; FFM, fat-free mass.
† Range.
TABLE 2. Correlations between measurements in the example sample

<table>
<thead>
<tr>
<th></th>
<th>BMI*</th>
<th>FM*</th>
<th>FFM*</th>
<th>% Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>0.85</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFM</td>
<td>0.33</td>
<td>-0.07</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>% Fat</td>
<td>0.67</td>
<td>0.93</td>
<td>-0.37</td>
<td>1</td>
</tr>
</tbody>
</table>

* BMI, body mass index; FM, fat mass; FFM, fat-free mass.

Subjects 95 percent of the total sample size. This data set was split roughly evenly between males (48 percent) and females (52 percent) (table 1), as well as between Africans (52 percent) and Americans (48 percent). All of the African subjects were human immunodeficiency virus (HIV)-seronegative employees of the National Bank of Zaire. The Americans were volunteers from the New York City metropolitan area. The body composition was measured by means of an RJL 101A bio-impedance analyzer with standard tetrapolar lead placement (RJL Equipment Co., Detroit, Michigan).

Hypothetical model

Using the actual data collected as described, we estimated what the shape of the BMI-mortality distribution would be assuming a hypothetical underlying model. Specifically, we assumed that the logit of the probability of death within some defined period of time could be characterized by model 1, i.e.,

\[ \text{Logit}(\pi) = \beta_0 + \beta_1 \frac{\text{FM}}{m^2} + \beta_2 \frac{\text{FFM}}{m^2}. \]

Assuming \( \beta_0 = 0 \) (we are not interested in the intercept but in the effects of FM and FFM), the probability \( \pi \) of death within the defined period of time can then be calculated for each subject as follows:

\[ \pi = P(D = 1|\text{FM}, \text{FFM}) = \frac{\exp(\beta_1 \frac{\text{FM}}{m^2} + \beta_2 \frac{\text{FFM}}{m^2})}{1 + \exp(\beta_1 \frac{\text{FM}}{m^2} + \beta_2 \frac{\text{FFM}}{m^2})}. \]  \hspace{1cm} (2)

It is also assumed that \( \beta_1 > 0 \) and \( \beta_2 < 0 \) (condition 1 and 2). To calculate the death probabilities, we set a range of the parameter sets of \( \beta_1 \) and \( \beta_2 \) as listed in the first two columns of table 3.

Methods

For each set of \( \beta_1 \) and \( \beta_2 \) individual probabilities of death were calculated according to equation 2. Subjects were then placed into bins of unit BMI length (i.e., 16 to <17, 17 to <18, 18 to <19 . . . 39 to 40).

At each BMI level, the % fat (PF) was averaged over all subjects in that interval as well as the calculated probability of death for each set of \( \beta_1 \) and \( \beta_2 \).

The average % fat was fitted by a quadratic regression onto BMI and BMI\(^2\), weighted by the sample size of each bin, as follows:

\[ \text{PF} = \gamma_0 + \gamma_1 \text{BMI} + \gamma_2 \text{BMI}^2. \]  \hspace{1cm} (3)

This model was postulated to see the statistical significance of the estimated coefficients for BMI\(^2\), and to verify the monotonic relation of % fat with BMI.

Based on the average death probability in each bin of BMI level, the odds ratio (OR) between each BMI level and the BMI level associated with minimum death probability was obtained and similarly fitted by the following weighted quadratic regression in terms of BMI level:

\[ \text{OR} = \alpha_0 + \alpha_1 \text{BMI} + \alpha_2 \text{BMI}^2. \]  \hspace{1cm} (4)

This model was tried to see if the odds ratios (generated by means of FM and FFM) can also be fitted by a (usually practiced) BMI-quadratic model.

Results

The resulting weighted quadratic regression (model 3) fit of PF is depicted in figure 1. There clearly appears to be a strong (monotonic increasing) linear relation between PF and BMI (\( R^2 = 0.977 \)); \( \gamma_1 \) was estimated as 1.37 (\( p = 0.011 \)) and \( \gamma_2 \) as 0.007 (\( p =

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0.475). Therefore, it is verified that the pooled sample meets condition 3.

For each set of $\beta_1$ and $\beta_2$ model 4 was fitted and the resulting estimates of $\alpha_0$, $\alpha_1$, and $\alpha_2$ are listed in table 3, along with the estimated BMI levels associated with minimum death probabilities (estimated from model 4). All of the coefficients were statistically significant with all $p$ values <0.0001. This indicates that the BMI-quadratic model fits the odds ratio very well even though these are generated by means of FM and FFM.

The resulting fits are depicted in figures 2a–5d. As can be seen, a U- or J-shaped relation clearly emerges between BMI and mortality depending on the sets of parameters through the absolute ratio $|\beta_1/\beta_2|$ of the two coefficients. Specifically, when the absolute ratio is small (a and b in figures 2–5), which implies that the negative effect of FM is relatively smaller than the positive effect of FFM, the relation becomes U-shaped. On the other hand, when the absolute ratio is large (c and d in figures 2–5), which implies that the negative effect of FM is relatively larger than the positive effect of FFM, the relation becomes J-shaped. This is quite intuitive in this hypothetical setting, because BMI is highly correlated with FM (correlation = 0.85, table 2); the large effect of FM might have been manifested directly through the highly correlated BMI. In addition, closer inspection of the BMI nadirs (the BMI associated with the minimum mortality) in table 3 reveals that they are also a function of the absolute ratio in this hypothetical example. That is, the combination of the effects of FM and FFM could be a factor in estimating the nadir in terms of BMI.

The overall pattern of the shapes of the BMI-mortality relations over the given range of the parameter sets is quite similar to that seen in actual studies of BMI and mortality. Again, we emphasize that the U- or J-shaped relation between BMI and mortality in this hypothetical example emerges despite the fact that the "true" (hypothetical) relation between fatness and mortality is monotonic increasing and the true (actual) relation between BMI and percent body fat is also monotonic increasing (figure 1).

DISCUSSION

We have suggested that the U-shaped relation frequently observed between BMI and mortality may result at least in part from the fact that BMI is composed of separate components, mainly FM and FFM, which have opposite effects on health and longevity. We have shown that even in the circumstances where adiposity expressed either as % fat or absolute FM increases monotonically with BMI and where risk of death increases monotonically with adiposity, this U-shaped relation between BMI and mortality can still emerge. This finding shows that the "clinical wisdom" that "one can never be too lean" is not inconsistent with the epidemiologic observation that "one can be too thin."

However, we must emphasize that we have only demonstrated that this is a plausible explanation for the frequently observed U-shaped relation. We cannot say with any degree of certainty that this is the actual explanation for the observed phenomenon. Nevertheless, such an explanation seems plausible. For example, Keys (41) found that, compared with individuals who died at 35-year follow-up, those who survived had greater body density but a somewhat smaller BMI.
on average. Decreased FFM has also been shown to coincide with the increased mortality of individuals exposed to traumatic life experiences involving starvation (49).

As stated above, research exists (18, 38–40) that indicates that body composition more than BMI is a primary determinant of health. Consistent with this hypothesis, some research (31, 50) has shown a somewhat more monotonic relation between adiposity as measured by skinfolds or circumferences and mortality than between BMI and mortality. In addition, Baumgartner et al. (51) have argued that the measure-
ment of body composition, rather than BMI, will ultimately shed the most light on this issue of mortality. They state, “Efforts to recommend ‘optimal’ weights, as well as cutoff values for underweight or overweight, deny the biological reality . . . that individuals of the same weight, or even weight-for-stature, can have widely differing amounts of fat and lean mass as well as fat distribution” (51, p. 90). The authors offer plausible theoretical relations among FM, FFM, and mortality risk which might yield the observed U- or

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FIGURE 4. Weighted quadratic regression fits of odds ratios of death probability onto body mass index (BMI) and its square. Each data point represents the odds ratio obtained from the average death probability, when $\beta_1 = 0.03$, for all scores falling within the given BMI bin with varying $\beta_2$: (a) $\beta_2 = -0.12$; (b) $\beta = -0.09$; (c) $\beta_2 = -0.06$; (d) $\beta_2 = -0.03$.

J-shaped association between BMI and mortality risk (51, figure 3, p. 91); however, those models differ from the one we propose here.

The most obvious implication of this conjecture is that, were it correct, meaningful inferences about the relation between adiposity and mortality would be better achieved by conducting prospective cohort studies that take actual measurements of body composition rather than by relying solely on BMI. In this regard, it is noteworthy that the third National Health and Nutrition Examination Survey (NHANES-III) measured body fat with bio-impedance analysis (52) and that
proposals for NHANES-IV include the measurement of fatness with dual energy x-ray absorptiometry (Steven B. Heymsfield, Obesity Research Center, St. Luke’s/Roosevelt Hospital, New York, NY, personal communication, 1996). Longitudinal follow-ups of these studies would therefore be enlightening. From a clinical point of view, such results would also suggest that weight loss would only be beneficial if the ratio of FM lost to FFM lost exceeds the absolute value of the ratio of $\beta_1/\beta_2$. This result also holds if the model
is expressed as a proportional hazards model (i.e., $h_i = h_0e^{\hat{\beta}_2FM_j + \hat{\beta}_1FFM_j}$). However, both assume (for this simple ratio statement to be true) that the logit or log hazard of death increase and decrease linearly with increasing FM and FFM, respectively. Were actual estimates of $\hat{\beta}_2$ and $\hat{\beta}_1$ available, these could be used to guide clinical practice by establishing under which methods and conditions of weight loss the ratio of FM to FFM lost exceeded the desired level. Treatment components that affect these changes (e.g., dietary composition, exercise regimen, etc.) could be investigated to examine the relative rate at which they produced changes in FM and FFM.

In conclusion, we have suggested an additional hypothesis, different from that of occult disease, to explain the U- or J-shaped relation observed between BMI and mortality. We concur with Baumgartner et al. (51) that future investigators should strongly consider conducting prospective longitudinal studies using actual measures of body composition rather than simply BMI.

ACKNOWLEDGMENTS

Supported in part by National Institutes of Health grant nos. ADDK353572, DK51716, DK26687, R29DK47256, DK42618, and T32DK37352.

The authors thank Drs. Richard N. Pierson, Jr., Steven B. Heymsfield, Angelo Pietrobelli, Donald Thea, Gerald T. Keusch, and Michael E. St. Louis for the use of their body composition data.

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