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Studies of the impact of age on optimal body weight

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The question of whether the range of recommended body weights should remain the same throughout adulthood or should be more liberal (higher) in older adults has been extremely controversial. Much of the debate has centered on methodologic issues including sources of confounding and the precision of risk estimates. These methodologic issues are reviewed, and studies that compare the body mass index (BMI)-mortality relationship within appropriate age strata are summarized. Several studies have attempted to control for major confounders, but were too small in size to produce comparisons across age groups. Only three studies had as many as 400 deaths in each age group, and only one of those attempted to control for confounding variables. This study, a recent analysis of the Cancer Prevention Study-I, combined attention to possible confounding variables with the statistical power that comes from a large sample. The analysis indicated that the optimum 12-year survival was associated with a lean BMI (19-21.9) between the ages of 30 and 74 years. After 74 years, the optimum BMI was considerably higher. This study had several limitations and its generalizability is restricted, but nevertheless, it offers the best evidence to date on the impact of age on the BMI-mortality association. New studies are needed that control for possible confounding factors and include repeated measures of weight and height, and perhaps other indicators of body composition and fat distribution, over a long period of follow-up. (J. Nutr. Biochem. 9:501–510, 1998) © *Elsevier Science Inc. 1998*

Keywords: obesity; age; epidemiology; review; mortality

Introduction

Americans tend to gain weight as they pass from early to mid-adulthood.[1] Recent national data from the National Health and Nutrition Examination Surveys (NHANES) III[2] showed that more than half (52%) of women between the ages of 50 and 59 years were overweight, whereas only 20% of women in their twenties were overweight. Similar figures for men were 42% and 20% in the older and younger groups, respectively.

The criteria used to define overweight in the report from the NHANES III survey[2] was a body mass index (BMI; weight in kilograms divided by the square of height in meters) value of 27.8 or more for men and 27.3 or more for women. These commonly used cutpoints are defined as the gender-specific 85th percentile values of BMI for men and women aged 20 through 29 years from NHANES II, and as such they were not founded on the basis of health, disease, or longevity. In contrast, the 1983 Metropolitan Life Insurance (MLI) Height and Weight tables were derived from studies of mortality. These widely quoted tables show desirable or optimal weight, defined as the weight-for-height associated with the lowest mortality. This type of information has traditionally been used to formulate weight goals and recommendations to the public. The NHANES II cutpoints represent approximately 124% of the desirable weight for men and 120% of the desirable weight for women, defined as the midpoint range of weights for a medium frame from the 1983 MLI Height and Weight tables, after appropriate adjustments for clothing and shoes.[3,4]

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This work was supported by R01 DK50776 from NIDDK.
This paper was delivered at the 23–25 October 1997 conference "The Determination, Treatment, and Prevention of Obesity," which was sponsored by the Institute of Nutrition, University of North Carolina at Chapel Hill; Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill; and School of Medicine, East Carolina University, in cooperation with the North American Association for the Study of Obesity, the National Institutes of Health, the American Cancer Society, and Eli Lilly & Company.
Received December 17, 1997; accepted February 24, 1998.

655 Avenue of the Americas, New York, NY 10010
0955-2863/98/$19.00
PII S0955-2863(98)00012-6

Neither the NHANES II cutpoint nor the MLI desirable weight distinguish between younger and older adults. The question of whether the range of recommended body weights should remain the same throughout adulthood or should be more liberal (higher) in older adults continues to be extremely controversial. The intensity of this controversy is evidenced by a series of letters to the editor in the *American Journal of Clinical Nutrition*[5–11] that were prompted by the *Dietary Guidelines for Americans*[12] released by the U.S. Department of Agriculture in 1990. For the first time the new guidelines included age-specific recommended ranges of weight-for-height, with heavier weights indicated for individuals 35 years of age and older. Age-specific weight recommendations were subsequently omitted form the 1995 Dietary Guidelines[13] presumably because of inadequate information to support the need for different recommendations.

Much of the discussion on the issue of age and optimal body weight centers on the methodologies used in the epidemiologic studies on this topic. This article reviews some of the methodologic issues that are pertinent to an analysis of the effects of body weight on mortality are explored and issues that are relevant to age. Studies that present age-specific analyses of the BMI-mortality relationship are reviewed in light of these methodologic traps. Finally, I address the question: Does age impact the BMI associated with the lowest mortality?

Methodologic issues

The method used to measure obesity has evolved over the years. Conceptually, most researchers would agree that percent body fat is the exposure of interest. However, percent body fat is not easily measured in large populations. Body weight, on the other hand, can be very easily and inexpensively measured in a variety of settings and is easily understood by the public. The difficulty with weight is that it must be adjusted for height. In early studies, researchers examined the effect of weight-for-height using several categories of height in increments of one inch, while more recently, BMI has been used to express weight relative to height. BMI is related to percent body fat with a correlation coefficient of approximately 0.7. The reciprocal of BMI (1/BMI) has been advocated for use in analyses by some investigators,[14,15] but currently BMI is the most commonly used measure in obesity research.

In 1987, Manson et al.[16] published a comprehensive review of studies on the relationship between body weight and mortality, most of which used BMI as an indicator of fatness. These studies showed no association, a positive association, a J- or U-shaped association, and even an inverse association between weight and total mortality. Reasons for these discrepant results cited in the review included lack of control for cigarette smoking, inappropriate adjustments for biologic effects of obesity, failure to control for cases that had experienced disease-induced weight loss, and inadequate statistical power. Additional issues that are pertinent to the analysis and interpretation of the BMI-mortality relationship, though perhaps less potent, are socioeconomic status (usually measured as educational level), nutrient and alcohol intake, physical activity, weight change, use of data from self-report, fat distribution, body composition, and the choice of age and/or BMI cut-points to form categories. The impact of each of these factors on studies of the BMI-mortality association are summarized below.

Smoking

Cigarette smokers tend to weigh appreciably less than do nonsmokers[14] but have higher rates of death because of their smoking. This phenomenon could create increased mortality for lighter people and shift the apparent optimal BMI toward a higher level.[16] Effects of smoking may be more exaggerated in older individuals because older individuals are likely to have smoked more years than their younger counterparts.

Mindful of the fact that cigarette smoking probably exerts an important effect on exposure and outcome, an attempt to control for cigarette smoking has often, but not always, been incorporated into the analytic methods used by investigators. It is not clear whether all of the traditional analytic strategies have been successful. There is concern that using multivariate analyses to adjust for the effects of cigarette smoking may leave "residual confounding" in the BMI-mortality relationship, and that stratified analyses that combine data from nonsmokers with former smokers may also result in inadequate control of this powerful variable.[17]

Biologic effects of obesity

Risk factors such as diabetes and hypertension are recognized mediators of the BMI-mortality relationship. However, these conditions are not true confounding variables, but effects of obesity and links in the causal pathway by which obesity exerts its influence on mortality risk.[16] When interest is in the overall true effect of obesity on risk, it is not fruitful to estimate the residual effect of obesity after eliminating known biologic mechanisms for transmitting weight-related risk.

Disease induced weight loss

Many diseases cause weight loss, and participants in studies of obesity may be at a weight lower than their usual adult weight as a result of diagnosed or undiagnosed illness at the time the baseline weight measurements were obtained. As with smoking, this phenomenon could also create increased mortality for lighter people and shift the apparent optimal BMI toward a higher level.[16] However, this effect is complex and depends on the distribution of weight in the diseased members of the population. For example, a disease induced lower body weight resulting in a BMI of 19 kg/m^2 would result in increased mortality at low BMI levels and also would flatten the slope of the overall BMI-mortality relationship by inflating mortality at the left-hand side of the BMI distribution. It could even (spuriously) cause a rise in mortality in individuals at the lowest end of the BMI distribution resulting in the not infrequently reported J- or U-shaped distribution curve. Alternatively, if an obese individual became ill and lost weight such that their BMI was still obese at the time of the study measurement, their death shortly after the initiation of follow-up could make a *less* obese weight appear more deadly and cause the curve to

become steeper. This scenario is not likely to occur in large numbers of participants, but it illustrates the complexity of the issue.

The impact of disease-induced weight loss on the analysis of the BMI-mortality relationship may likewise be inflated in older individuals because at older ages, the diseases associated with weight loss are more common. Because data on weight loss are rarely available, a common method used to control for this effect is to delete from the analyses participants who died within 1 year or a few years of the weight measurement.[18] This is a crude method for this purpose, and obviously results in the concurrent deletion from the analyses of some number of cases who had neither disease nor disease-induced weight loss at the time of the baseline measurement. In order to cause confounding, a variable must be associated with both the outcome (here death) and the exposure (here BMI). If subjects have a disease at baseline, but have not experienced disease-induced weight change, then the disease does not confound the BMI-mortality relationship.

Lack of statistical power

A common, but often difficult to overcome, weakness in epidemiologic studies of obesity is inadequate sample size or length of participant follow-up. The mortality risk associated with obesity is not so high that it can be easily detected with small samples. Sjostrom[19] concluded that all-cause mortality was approximately doubled by obesity. He observed that studies that found no effect of obesity on mortality usually examined small samples ($n < 7{,}000$) and/or were of short duration (less than 5 years). Manson et al.[16] asserted that only four studies they reviewed had at least 90% statistical power to detect a 20% or greater difference in mortality between quintiles of weight groups. These studies were the first Cancer Prevention Study (CPS-I),[20] the Norwegian study,[21] and the 1959 and 1979 Build Studies.[3,22]

The number of years of follow-up can affect the number of events and therefore the power of the analysis. It can also influence the relative mix of causes of death, in combination with age and complex issues involving competing causes of death. For instance, cardiovascular disease mortality is higher in African-American men than in white men at younger ages, but less than that of white men at more advanced ages.[23] It has been speculated that this decline is due to the removal of African-American men susceptible to cardiovascular disease from the pool of deaths at older ages.

The issue of statistical power takes on added importance in studies that attempt to compare the BMI-mortality relationship across age groups. The author and colleagues have previously reported that it takes approximately 400 events in each age group to detect a ratio of hazard ratios of 1.5 using BMI as a dichotomous variable divided at the median.[24] For example, assuming $\alpha = 0.05$ and $\beta = 0.2$, approximately 400 deaths would be required in each age group to detect a difference in the relative risk of mortality above versus below the median BMI of 1.33 in one age group and 2.0 in another.

Education

Though likely much smaller than the effect of smoking or disease-induced weight loss, lack of control for educational level may confound the BMI-mortality relationship. Low levels of education are associated with higher levels of mortality and, at least in women, higher levels of body weight. Thus, confounding by educational level could result in an overestimation of the effect of obesity on mortality. There is also some evidence that the effects of thinness on mortality could depend on socioeconomic status—a variable often represented by educational level. Tayback et al.[25] found that an excess risk of mortality with low weight was seen only in women aged 65 to 74 years who were living in poverty. These findings suggest that the relationship of thinness to mortality could also be different at different levels of socioeconomic status or education.

Nutrient and alcohol intake

On average, obese individuals consume more calories than do thin individuals, although correlations between weight and reported caloric intake are often weak. Similarly, individuals who consume alcohol also tend to consume more calories than nondrinkers;[26] however, the associations between alcohol intake and body weight are not clear.[27,28] Overall mortality rates tend to be lower in individuals who consume moderate amounts of alcohol compared with nondrinkers or persons who consume in excess of four drinks per day.[29] An explanation for these nonlinear associations is that confounding may exist among alcohol consumption, body weight, and mortality. The impact of alcohol may differ by age, as older adults tend to consume less alcohol than younger adults.[30]

Physical activity

Physical activity may also be a confounder of the BMI-mortality relationship in that it is associated with body weight[31] and with mortality risk.[32,33] It is usually assumed that the association between physical activity and body weight is due to the influence of exercise on body weight. However, there is some evidence that the pathway may be multi-directional; that is, the level of body weight may also influence the level of activity. Thus, physical activity could function both as a confounder of the BMI-mortality relationship, and to some extent, as a mediator of the effect of weight on mortality if, for instance, heavier individuals do not exercise because of perceived societal expectations that people who exercise should be thin. It is well documented that older adults tend to be less physically active than younger adults.[34,35]

Changes in weight over time

In most studies of the BMI-mortality relationship, BMI is estimated at only one point in time and at one age for each participant. Thus, the study design does not allow age effects to be distinguished from secular or birth cohort effects, and no conclusions can be drawn about the impact of changes in weight. Currently uncertainty surrounds the influences of sustained intentional changes in weight and of

weight cycling. Despite indications from multitudinous short-term studies showing beneficial effects of intentional weight loss, convincing long-term studies of the benefits of weight loss on mortality are lacking. At present, no definitive conclusions can be drawn regarding the effects of intentional weight change on longevity.[36–38] It seems likely that older adults would be less likely to intentionally lose weight than younger adults.

Data from self report

Many studies of the BMI-mortality relationship use recalled data for height and weight. These include (but are not limited to) the Nurses Health Study, the Seventh Day Adventist Study, the Harvard Alumni Study, and CPS-I. Several investigators[39–44] have examined the validity of self-reported height and weight. In general, self-reported height and weight have been found to be highly correlated with the measured variable with correlation coefficients above 0.9. Nevertheless, there is bias in data from self-report because lighter subjects tend to overestimate their weight and heavy subjects tend to underestimate their weight. Though data from self-report is useful, this bias makes measured data for height and weight highly preferred.

Fat distribution and body composition

Finally, the confounding effects of body fat distribution and body composition on evaluating the risk of death should be considered. Several studies have shown fat distribution to be predictive of mortality, and some have shown it to be a better predictor than BMI. BMI and waist-to-hip ratio are correlated within gender and the relative importance of each needs more study. In the Health Professionals Follow-up Study, waist-to-hip ratio was a significant predictor of incident coronary events in men 65 years of age and older, while BMI was not.[45] The correlation between BMI and both subscapular skinfold thickness[46] and waist-to-hip ratio[45] declines with age. Thus, BMI may be a less useful indicator of total fatness and fat patterning in older individuals, and this could attenuate mortality relationships in older individuals. In addition, older adults are likely to have less muscle mass versus fat mass[47] and more abdominal fat[48,49] than younger adults at the same BMI. This relationship could potentially make a given level of BMI appear more deleterious in older than younger adults because the given level of BMI would represent greater adiposity in older adults.

Cutoff points

The existing studies of BMI and mortality use a variety of cutoff points to categorize BMI and age. The width of the age ranges is often dictated by the sample size, which necessitates combining subjects of different ages in order to have an adequate number of events. Likewise, cutpoints for BMI are often "data driven" quartiles or quintiles. The use of quartiles or quintiles for the study of BMI can be problematic because extremely thin subjects are usually combined with subjects of hypothesized optimal weight. These cutpoints of convenience may have a profound effect on the associations they are trying to measure. The death rate in the lowest category may be elevated due to the inclusion of extremely thin subjects in the category, and the elevation of the death rate in the reference category could attenuate the apparent effect of obesity.

Table 1 BMI associated with lowest mortality within age groups in analyses reported by Andres et al.[50]

Age group (years)	BMI (kg/m^2)	
	Men	Women
20–29	21.4	19.5
30–39	21.6	23.4
40–49	22.9	23.2
50–59	25.8	25.2
60–69	26.6	27.3

Review of studies

Studies that compare the BMI-mortality relationship within appropriate age strata have the strongest potential to offer evidence for or against the usefulness of age-specific guidelines on optimal body weight. These types of studies are discussed below in terms of the methodologic strengths and weaknesses outlined in the previous section. Pertinent studies are summarized, and the author's recent analyses of the BMI-mortality relationship in the CPS-I cohort presented in some detail.

The Build Study

The most outspoken proponents of the hypothesis that optimal weight increases with age have been Rubin Andres and his associates. Indeed their publication of a re-analysis of the Build Study 1979[50] appears to be the work that sparked the controversy in this area. They used data from 4.2 million insurance policies issued from 1950 to 1971 and traced to 1972 that were collated from 25 life insurance companies in the United States and Canada. There were 106,000 deaths among the subscribers during this period. Mortality ratios (actual:expected deaths) were included in the report for each gender by decade. Andres et al.[50] used these reports (not the original data) to estimate BMI (kg/m^2) and modeled the BMI-mortality relationship for five age groups. They found the best fit for their data when a quadratic term (BMI^2) was included in the regression model. Parabolic curves for each age category were constructed for each gender and the nadirs of the U-shaped curves were computed. The nadir corresponded to the BMI associated with the lowest mortality. As shown in *Table 1*, the BMI associated with the lowest mortality was higher at older ages in both men and women. In the oldest age group examined, the weight associated with the lowest mortality would be considered overweight by some standards (cut point from NHANES II 27.3 kg/m^2 for women and 27.8 kg/m^2 for men).

Andres and colleagues' review of studies

Andres et al.[50] also published a re-examination of data from 23 populations that had been presented in the literature with

adequate detail from which to ascertain the BMI value associated with the lowest mortality within age groups. A total of 65 age-specific values were calculated in men and 33 in women. These values were compared with the mid point of the recommended weight for a medium frame at a given height in the 1959[51] and the 1983[52] MLI tables. Using the 1959 tables (which recommended a lower weight-for-height than the 1983 tables), the MLI recommended weight-for-height was lower than the BMI associated with the lowest mortality in over 90% of the groups examined. Using the 1983 tables, the MLI recommended weight-for-height was lower than that associated with the lowest mortality in approximately 85% of the groups. The authors noted that in six of the eight groups in which the MLI recommended weight represented a BMI that was higher than they had calculated to be associated with the lowest mortality, the subjects were below the age of 40 years. They did not report the ages of the groups that fell on either side of the 1983 recommendations.

The Norwegian experience

Another very large study that examined the impact of age on the BMI-mortality relationship was conducted in Norway between 1963 and 1979.[21] The analyses presented were based on 1,717,515 participants, of whom 176,574 died during the approximate 10 years of follow-up. The percent deceased within BMI level was calculated in each of 14 age groups in both men and women. Values were plotted with the percent deceased (the y-axis) expressed on the log scale. *Figure 1* shows the plot from men as it was published in the original manuscript. In the plot of data from men, as well as in the plot of data from women (not shown), the BMI-mortality relationship was U-shaped in the younger groups and became flatter with age. *Figure 2* shows the same data re-plotted without the log scale. Examination of *Figure 2* shows that the relationship between BMI and mortality was rather flat in the younger groups, takes on a U- or J-shape in middle age, and then becomes somewhat erratic in the oldest age groups. There does not appear to be any evidence that the nadir of the U-shaped curves is at higher BMI levels (shifted to the right) with increasing age. In fact, the nadir appears to be at a lower BMI in the 50- to 64-year-old groups than in the 30- to 49-year-old groups.

The National Health Examination Epidemiologic Follow-up Survey

The National Health Examination Epidemiologic Follow-up Survey (NHEFS) study[25] included far fewer participants than the Build Study or the Norwegian Study. In NHEFS, 4,710 American men and women in two age groups (55–64 and 65–74 years) were followed for vital status over an average of 8.7 years. The investigators controlled for smoking using multivariate analyses and controlled for disease-induced weight loss by excluding participants who died in the first year of follow-up. There was a trend toward increased risk of death at the high end of the BMI continuum in the younger group and at the low end of the BMI continuum in the older group. However, all the confidence intervals included 1.0.

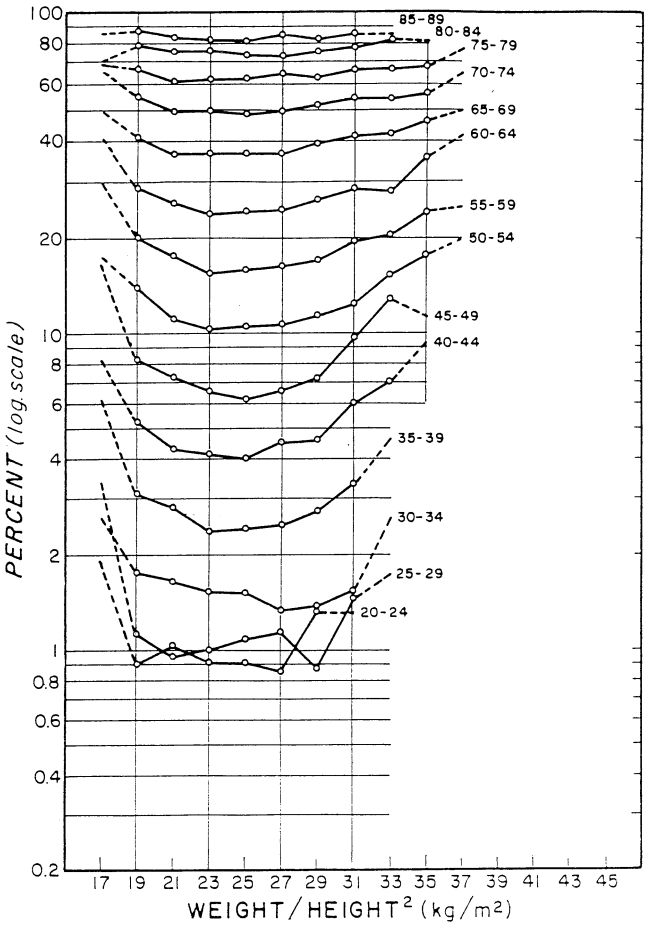

Figure 1 Log of percent of women that died over approximately 10 years of follow-up by BMI and age groups in a Norwegian cohort (from Waaler).[21]

Male British civil servants

The relationship between BMI and mortality was examined in three age groups (40–49, 50–59, and 60–64 years) in 18,403 male, British civil servants in the Whitehall Study.[53] Smoking was controlled by stratification, but there was no control for disease-induced or unintentional weight loss. No association was found between BMI and cardiac heart disease mortality rates in the oldest age group of never-smokers or current smokers, whereas significant positive associations were seen in the younger age categories.

Finnish women and men

Rissanen et al. studied the BMI-mortality relationship in 17,159 Finnish women[54] and 22,995 men[55] aged 25 years and older at entry. Subjects were followed for a median of 12 years. In the analysis of the data from women, the authors attempted to control for disease-induced weight loss by excluding participants with a history of heart disease or cancer at baseline and by doing separate analyses of deaths that occurred in the first 7 years of follow-up (half the person-years at risk). Nonsmoking women ages 25 to 64 years had a U-shaped relationship between BMI and all-cause mortality. The relative risk was 1.7 [95% confidence

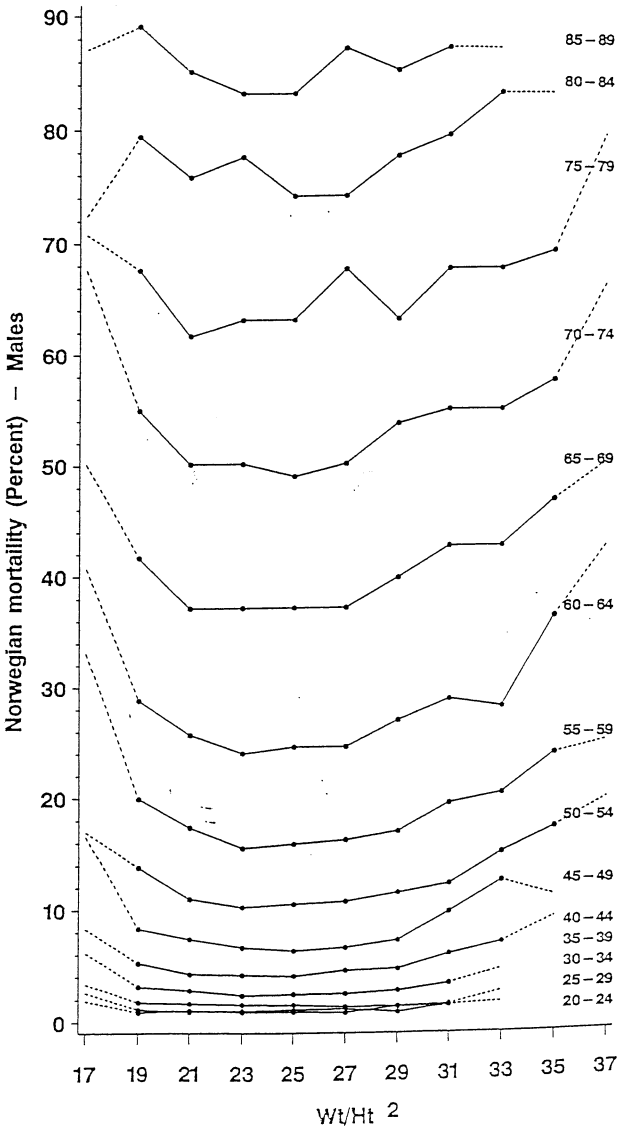

Figure 2 Percent of women that died over approximately 10 years of follow-up by BMI and age groups in a Norwegian cohort (adapted from Waaler).[21]

interval (CI) 1.2–2.3] for the first compared with the second quintile of BMI and 1.8 (95% CI 1.2–2.2) for the fifth compared with the second quintile. Similar patterns of risk were not seen in women over 65 years. The relative risk estimate for the first versus the second quintile of BMI was 1.1 (95% CI 0.9–1.4), and for the fifth versus the second quintile of BMI the relative risk estimate was 1.0 (95% CI 0.8–1.2). Analogous, though not identical, estimates were presented for men for all-cause, cardiovascular, and cancer mortality and are summarized in *Table 2*. In men the effects of smoking were controlled through the analysis, and participants with a history of heart disease and cancer were not excluded. The BMI-mortality relationship tended to be U-shaped for all-cause and cardiovascular disease mortality in the younger men, and the effects of BMI tended to be diminished in the older age group, although the relative risk estimates for all-cause mortality in obese men (BMI $\geq$ 31) were 1.2 in both age groups.

The Finnish studies provide no evidence that the impact of obesity on mortality is different in adults over 55 years of age compared with younger adults. The increased risk of death among adults aged under 55 years with BMI values under 22 could be due to disease-induced weight loss or to smoking, although some attempts were made to control for both of these factors. Different strategies were used to control for these sources of confounding in women and men; however, neither study had rigorous control of confounders. For example, women current smokers were excluded but former smokers were retained. In the men's data, smoking was controlled by statistical adjustment, which can leave residual confounding. It is possible that the increase in death rates in subjects with a BMI less than 22 was driven by subjects with BMI levels below 19; however, this cannot be determined from the data presented.

Seventh-Day Adventist women

The relationship between BMI and mortality was examined over a period 26 years of follow-up in California Seventh-Day Adventist women. Height and weight were collected by self-report in 1960, and vital status was obtained over the subsequent 26-year period. The analysis was restricted to never-smoking white women and separate analyses were shown for women of stable weight with no major chronic disease or severe physical complaint at baseline (n = approximately 7,000). The 26-year follow-up period was divided into segments because the hazard rates fluctuated

Table 2 Relative risk[1] (95% confidence interval) of mortality from all causes, cardiovascular disease, and cancer by age and BMI groups in Finnish men

	Age 25–54 years			Age ≥55 years		
	BMI <22.0	BMI 22.0–24.9	BMI ≥31.0	BMI <22.0	BMI 22.0–24.9	BMI ≥31.0
All causes	1.2 (1.0–1.5)	1.0	1.2 (0.9–1.7)	1.1 (0.9–1.3)	1.0	1.2 (1.0–1.5)
Cardiovascular causes	1.4 (1.0–1.8)	1.0	1.6 (1.0–2.4)	0.9 (0.7–1.1)	1.0	1.4 (1.1–1.8)
Cancer	1.7 (1.1–2.6)	1.0	1.1 (0.6–2.3)	1.4 (1.0–1.8)	1.0	1.0 (0.6–1.6)

[1]Age, geographic region, and smoking adjusted for in the analysis. Duration of follow-up was >7 years. Adapted from Rissanen et al.[55]

over time. Among women aged 30 to 54 years at baseline, there was a weak linear relationship between BMI and mortality during the first 8 years of follow-up, a significant linear relationship during years 9 through 14, and a significant U-shaped relationship during years 15 through 26. Among women aged 55 to 74 years at baseline, there was a significant U-shaped relationship during years 1 through 8 and a significant linear relationship during years 9 through 14 and 15 through 26. The relative risk in the fifth compared with the first quintile of BMI tended to be higher in younger women compared with older women. For example, with 9 to 14 years of follow-up, the relative risk of mortality in the fifth quintile (BMI $>$ 27.4) compared with the first quintile (BMI $<$ 21.3) was 4.02 (95% CI 1.54, 10.5) in the 30 to 54-year-old women and 1.24 (95% CI 0.85, 1.82) in the 55- to 74-year-old women. Thus the BMI-mortality relationship varied with both age and number of years of follow-up, but the relative risk associated with obesity tended to be larger in younger women.

Cancer Prevention Study-I

A portion of the Seventh Day Adventists in the work summarized above were also members of the CPS-I cohort of over 1 million Americans. The author and colleagues recently reported an analysis of the impact of age on the BMI-mortality relationship using the original 12 years of follow-up data obtained on the entire CPS-I cohort.[24] In this analysis, we attempted to avoid the methodologic weaknesses found in earlier work. The 62,116 men and 262,965 women included in this analysis were never smokers, had no history of heart disease, stroke, or cancer (other than skin), and had no history of recent unintentional weight loss. Participants who reported being sick or in poor health were also excluded, as were cases who died in the first year of follow-up. Unfortunately, measured anthropometric data were not available and height in inches (without shoes) and weight in pounds (in indoor clothing), as well as educational level, physical activity level, and alcohol consumption were collected by self-report.

Associations between BMI and mortality were examined within six age groups in models that adjusted for age in addition to educational level, physical activity, and alcohol consumption (*Figure 3*). In analyses that examined BMI in seven categories, the 19 to 21.9 BMI category was consistently associated with a low level of relative risk of death in men and women between the ages of 30 and 74 years. The pattern was less clear over the age of 74 years.

BMI was also examined as a continuous variable with BMI^2 initially included in the series of models to test for the presence of a U- or J-shaped curve. In men, the BMI^2 term did not reach the 0.05 level of significance in participants between the ages of 30 and 74 years. Among women in the same age range, BMI^2 was significant for all-cause mortality in the 30- to 44-, 55- to 64-, and 65- to 74-year-old groups, but not in the 45- to 54-year-old group.

Although the BMI^2 term was significant in some age groups among women, the difference between the level of risk predicted by the linear versus the quadratic models was small. We examined the size of the differences in the risk ratios at seven BMI levels when the full model was fit with

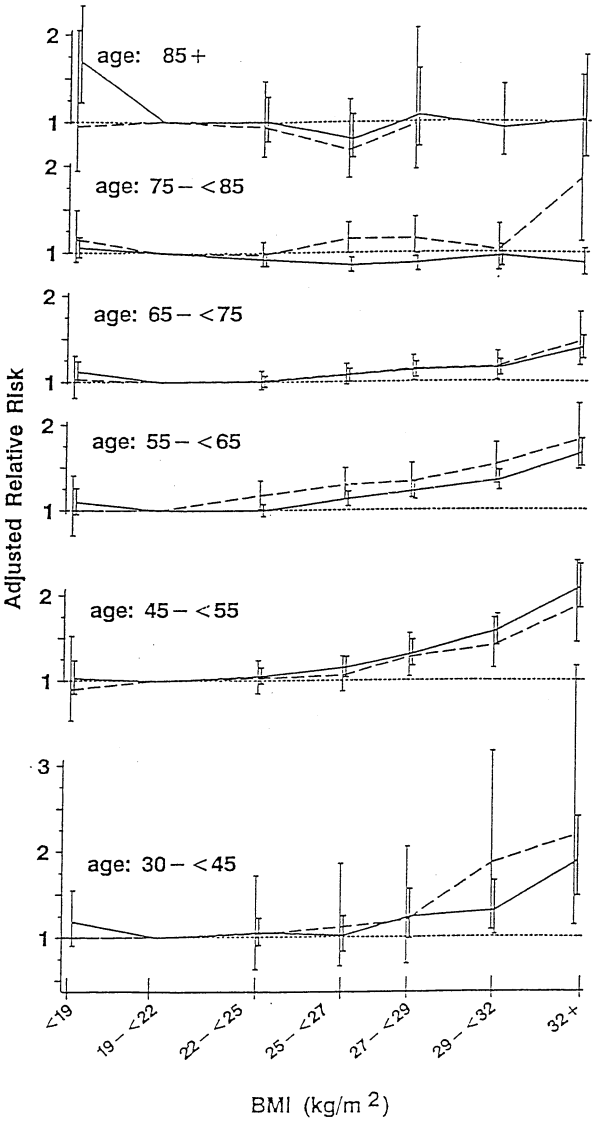

Figure 3 Relative risk of all causes of mortality by age and BMI groups in healthy, never-smoking white men (– – –) and women (—) in the CPS-I cohort. All relative risks have been adjusted for age, education, physical activity, and alcohol consumption. The reference category was made up of subjects with a BMI of 19.0 to 21.9. The bars represent 95 percent confidence limits. Relative risk estimates were not shown for points with five or fewer deaths. (from Stevens et al.).[24]

or without the quadratic term. The mean BMI for the age group was used as the reference. These analyses generated a total of 28 risk ratios at seven BMI levels in each of four age groups (*Table 3*). Differences in risk ratios of greater than 10% were found in only two estimates among women aged less than 75 years. Therefore, it made little difference whether a quadratic or linear model was used in the analysis, because the risk estimates across the relevant range of BMI were very similar. This finding was explained in part by the fact that the nadir of the U-shaped curve was at BMI levels below 20 in women aged less than 74 years (*Table 4*). Thus, the relationship between BMI and mortality was monotonic throughout the vast majority of the physiologic range of BMI.

Table 3 Percent of difference[1] in the relative risk estimates,[2] calculated using the linear versus quadratic models in women from CPS-I

	Age group			
BMI	30–<45	45–<55	55–<65	65–<75
<19	17.8	4.0	7.7	5.8
19–<22	7.7	2.0	3.9	2.8
22–<25	0.8	0.5	1.1	0.7
25–<27	−2.4	−0.3	−0.3	−0.2
27–<29	−3.1	−0.6	−0.6	−0.3
29–<32	−1.8	−0.4	−0.2	0.4
32+	7.2	1.1	3.0	3.8

[1]Percent difference calculated as (relative risk from quadratic model − relative risk from linear model) × 100/relative risk from linear model.
[2]Relative risk estimates were obtained using Cox proportional hazards models, which included age, education, physical activity, and alcohol consumption as covariates.

As previously reported[24] BMI (as a linear term) was associated with all-cause and cardiovascular disease mortality in men and women up to 75 years of age. However, the relative risk associated with BMI declined with age for both all-cause and cardiovascular disease mortality. For example, for all-cause mortality the relative risk associated with a one unit increment in BMI was 1.07 for 30- to 44-year-old men and 1.03 for 65- to 74-year-old men. For women the same relative risk estimates were 1.04 and 1.02, respectively. The interaction between BMI and age was examined using proportional hazards regression analysis that included covariates for education, physical activity, and alcohol consumption. Interactions were tested using BMI as a continuous variable and age as a continuous or alternatively as a categorical variable using six levels. The interactions were statistically significant in both men and women ($P < 0.001$ for all). The direction of the interactions indicated that the relative risk associated with BMI was smaller at older ages.

This study indicated that optimal survival over a 12-year follow-up was observed in participants who were at lean weights at baseline, and there was no tendency for the BMI associated with the lowest mortality to rise with age up to 74 years of age. The 19 to 21.9 BMI category was consistently associated with low risk. This BMI category includes participants who would be judged "slender" by common standards and is approximately equivalent to 90% to 100% of desirable body weight according to the 1983 MLI tables.[52]

Table 4 Body mass index associated with lowest relative risk as estimated by the quadratic model in women from CPS-I

	All cause mortality		CVD mortality	
Age	Nadir (kg/m^2)	p^1	Nadir (kg/m^2)	p^1
30–44	20.9	0.003	21.4	0.007
45–54	−5.6	0.1	−82.5	0.6
55–64	13.5	0.001	0.5	0.1
65–74	18.3	0.003	18.8	0.007
75–84	29.9	0.02	29.7	0.02
85+	28.1	0.048	30.4	0.5

[1]p-value is the BMI^2 term in model that included linear term for BMI and adjusted for age, education, physical activity, and alcohol consumption.

In women and men aged 75 years and older, there was little evidence that this low level of BMI was associated with optimal 12-year survival. In women aged 75 years and older, the relationship between BMI and mortality was U-shaped with the nadir of the U-shaped curve at 27.4 in 75- to 84-year-old women, and at 28.5 in women over 85 years. In men, the relative risk associated with BMI tended to increase only at high levels of BMI (≥32) (see *Figure 3*). There was an inadequate number of observations on which to base conclusions in men aged 85 years and older.

The limitations of this study have been summarized previously.[24] The numerous exclusions used in this analysis limit the generalizability of these results but increase the internal validity. The generalizability of the data from this cohort is suspect in any event, because participants were recruited as a convenience sample.[56] The sample studied represents an informative subset of the population similar in many characteristics that may confound the BMI-mortality relationship including gender, ethnicity, smoking, and poor health.

It is possible that the exclusions used here contributed to the absence of a rise in the risk of mortality at low levels of BMI (a J- or U-shaped association). Manson et al.[57] showed that the J-shaped relationship seen between BMI and mortality in women in the Nurses Health Study was no longer present after smokers, former smokers, and deaths within the first 4 years of follow-up were excluded from the analysis. In the remaining women there was no evidence of increased risk of mortality at low levels of BMI and the impact of BMI on mortality was monotone.

In this analysis, some types of confounding were prevented or reduced by exclusions and through the inclusion of covariates in the analyses. There were other limitations that could not be entirely overcome given the data at hand. These limitations include lack of measured data on height, weight, fat patterning, and body composition, measurement of BMI at only one point in time, the age of the data, and the limited number of years of follow-up.

Over the years since the CPS-I data were collected, there have been changes in the overall and cause-specific death rates in the United States.[58] The use of antihypertensive drugs and cholesterol-lowering drugs has greatly expanded, and numerous medical advancements have been made. The data from the CPS-I cannot reflect these changes. In addition, although these analyses imply that at a given level of obesity the associated increased risk of death may be lower in 65-year-old men than in 35-year-old men, it is possible that many men susceptible to the risks of obesity do not reach the age of 65 years, and thus 65-year-old men may represent a relatively obesity-resistant group.

Finally, the limited number of years of follow-up available in this study impact the interpretation of results. The 12-year mortality experience of a cohort of 30-year-old men and women is extremely different from that of 85-year-old men and women. There is evidence to indicate that BMI tracks throughout adult life[39] and little reason to believe that the impact of BMI on mortality is limited to 12 years in young adults. Indeed the impact of obesity on mortality is

probably not well captured by only 12 years of follow-up in young adults.

Conclusion

To address the question of whether age impacts the BMI associated with the lowest mortality, the ranges of BMI associated with the lowest level of risk within age groups must be identified and compared. Confounding, cutpoints used to define BMI and age, and the precision of risk estimates all heavily influence analyses that address this question. Evaluation of the literature on the impact of age on the BMI-mortality relationship requires careful attention to methodologic detail. In this literature no two studies were analyzed alike—even studies by the same authors.[54,55] Only three studies have been presented that had as many as 400 deaths in each age group[21,24,50] and only one of those attempted to control for confounding variables.[24] Andres and colleagues' analysis[50] of the Build Study and Waaler's analysis[21] of the Norwegian Experience had adequate statistical power, but did not control for cigarette smoking, disease-induced weight loss, and other potential confounders. Age-specific analyses of men and women in the NHEFS,[25] male British civil servants study,[59] a study of Finnish men and women,[54,55] and an extended study of Seventh Day Adventist women[60] were better controlled, but the number of deaths in each age group was small. Comparisons of risks across age groups were often not formally tested, and results within age groups were often not statistically significant. Lack of significant results are difficult to interpret when statistical power is low. Therefore conclusions from these studies are limited.

Because of its size and careful attention to possible confounding variables, the analysis of the CPS-I data set presented above appears to provide the best information to date to answer this question. That study indicated that the optimum 12-year survival was associated with a lean BMI (19–21.9) between the ages of 30 and 74 years. After 74 years, the optimum BMI was considerably higher. As noted above, this study had several limitations and its generalizability is restricted. New studies are needed that attend to possible confounding factors and include repeated measures of weight and height, and perhaps other indicators of body composition and fat distribution, over a long period of follow-up.

Acknowledgments

The author thanks Ms. Joy Wood, Ms Katherine Paton, and Dr. Jianwen Cai for their contributions to this work.

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