Overweight, Obesity, and All-Cause Mortality

To the Editor: Dr Flegal and colleagues[1] concluded that grade 1 obesity was not associated with higher all-cause mortality and that overweight was associated with significantly lower all-cause mortality. Other studies have shown that obesity in different populations, such as elderly people and patients with cardiovascular diseases, is also paradoxically not associated with a higher but rather with a lower mortality risk.[2] This has been termed the *obesity paradox*. The study by Flegal et al extends these findings to the general population.

The apparent paradox may be due to the use of the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) because it provides an inadequate definition of obesity. It does not take into consideration body composition (fat mass and fat-free mass) and can underestimate the degree of adiposity and its distribution. Although weight is correlated with body fat, it is also correlated with the amount of lean mass individuals have. Therefore, muscular individuals may be classified as overweight or even obese when BMI is used.

In aging and in conditions such as malignancy or rheumatoid arthritis, lean body mass may be lost while fat mass is preserved or even increased.[3] Thus, the relationship between age-related reduction of muscle mass and strength is often independent of body mass. Moreover, spontaneous weight loss is an accepted criterion of age-associated frailty.

Flegal et al[1] found an association between all-cause mortality and overweight and obesity by using an inaccurate method—BMI—for their classification. Villareal et al[4] proposed a definition of obesity as "an unhealthy excess of body fat, which increases the risk of medical illness and premature mortality." Direct estimates of total fat mass should provide a more accurate body assessment. It has been shown that, for the general population, in addition to BMI, waist circumference and waist-to-hip ratio are of importance for assessing mortality risk.[5]

Consequently, even though it is widely accepted, classifications of obesity based on BMI are inadequate.

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To the Editor: In a report on the association of overweight and obesity with all-cause mortality,[1] the authors' conclusions are incomplete because 2 major implications of the findings were not addressed.

First, the subgrouping by age showed that the association between obesity and mortality was attenuated with higher age. In fact, none of the various categories of BMI remained significantly associated with mortality in patients aged 65 years or older.

Weight management recommendations for the general population are needed that take into account advanced age. These data are in line with previous reports[2,3] of a decreasing association between overweight and obesity and mortality with advancing age. One study[4] found that obesity-related excess mortality declines with age at all levels of obesity, but it is particularly pronounced in very obese persons.

Second, the results by Flegal and colleagues[1] suggested a threshold for increased mortality at a BMI of 35 or greater. However, because the authors only reported a combined analysis of all patients with BMIs of 35 or greater, the increased mortality in this population may be driven by the most obese patients (grade 3), whereas patients in the lower grades may not have increased mortality. This result was shown for the subgroup with grade 1 obesity (BMI of 30-<35) but was not analyzed in detail for higher BMI subgroups.

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Therefore, it remains unclear if grade 2 obesity alone would carry a significant mortality risk. It would be clinically useful to identify the true threshold for obesity becoming a significant mortality factor.

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To the Editor: Dr Flegal and colleagues[1] conducted a systematic review and meta-analysis to assess the relationship between all-cause mortality, overweight, and obesity. Although the authors concluded that grade 1 obesity was not associated with higher mortality, and overweight was associated with lower all-cause mortality, some aspects of the study must be considered to better understand these controversial findings.

Inconsistency among selected trials was high, even after categorization of age and measured or self-reported weight. The authors attempted to reduce heterogeneity by using a sequential approach that excluded the outlier trials with more heterogeneity until a desired threshold of I^2 was reached.[2]

This approach is based on an erroneous interpretation of the I^2 statistic because it does not measure the magnitude of the between-study heterogeneity. This magnitude is determined by the between-study variance, often called τ^2, which was not shown by the authors. Additionally, reducing I^2 does not necessarily imply that the among-study variation will be diminished.[3]

As some other authors suggest,[4] the clinical relevance of any heterogeneity present in a meta-analysis is properly described through use of the τ^2 value. In contrast to the I^2 statistic, τ^2 does not increase with either the number or size of studies.

Therefore, presenting the τ^2 value could better identify the magnitude and clinical relevance of the heterogeneity found by Flegal et al.

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To the Editor: Dr Flegal and colleagues[1] reported a beneficial association between being overweight and survival in a large cohort of general population adults. One study[2] found a 20% and 30% improvement in 30-day and 1-year survival, respectively, among both overweight and obese patients admitted to an intensive care unit. Other studies (see citations in [2]) reported better survival (the obesity paradox) among obese patients with chronic diseases such as heart failure, chronic kidney disease, and human immunodeficiency virus/AIDS compared with normal weight patients.

The mortality risk that was attributed to overweight and mild obesity in earlier studies could be explained by associated risk factors, such as hypertension and hyperlipidemia, which were not always well-controlled in the past. The positive association between a BMI in the 25 to 35 range and survival in recent studies may be explained by the fact that improved control of these risk factors unmasked the survival benefits of overweight and mild obesity.

The first use of BMI to define overweight in the United States set a threshold of 27.8 for men and 27.3 for women and was based on the 85th percentile of BMI distribution among 20- to 29-year-olds, not on mortality data.[3] The threshold for defining overweight was reduced to a BMI of 25 in 1998 and became concordant with World Health Organization thresholds.[3]

The linkage to mortality occurred through the Metropolitan Life Insurance actuarial reports. But these reports ignored the fact that their data showed that adults older than 40 years with BMIs 10% to 20% above the ideal (the BMI range of 25-30) had better survival than those at ideal body weight.[4]

So it is not clear whether the assumption that being overweight or mildly obese was ever a mortality risk, and it is possible that the so-called obesity paradox was never paradoxical.

We agree with Drs Heymsfield and Cefalu[5] that "Not all patients classified as being overweight or having grade 1 obesity . . . require weight loss treatment." But we also wonder if it is time to simply reject the notion that being overweight or mildly obese is always bad for patients and to stop hounding such patients about their weight. If overweight patients keep their risk factors in control, they may outlive their lean friends.

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Disclaimer: The opinions expressed in this letter are the authors' own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the US government.

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To the Editor: In their meta-analysis of BMI and mortality "to inform decision making in the clinical setting," Dr Flegal and colleagues[1] found that mortality was not increased up to a BMI of less than 35.

We believe their study is flawed. Their comparison group (BMI of 18.5-<25) contains persons who are lean and active, heavy smokers, frail and elderly, and seriously ill with weight loss due to their disease, as well as Asian populations historically undernourished and burdened by infectious diseases.

Because the overweight (BMI of 25-<30) and obese (BMI of ≥30) groups are compared with this heterogeneous group possibly enriched with those at high risk of dying, the relative risks for the higher BMI groups are underestimated, creating an artifact of reduced mortality in the overweight group. Statistical adjustment cannot address this issue adequately because details of previous weight loss, smoking behavior, clinical conditions, and age were not available.

Flegal et al did not provide results for adults younger than 65 years, which is important because the relationship between BMI and mortality is much stronger at younger ages than in adults older than 70 years, probably due to the large loss of lean mass and greater influence of illness on weight. Thus, the results may reflect weight loss caused by disease and may not apply to generally healthy populations, and therefore may not be useable for clinical guidance.

To clarify the effects of body weight on mortality, 2 studies have pooled the primary data from 19 and 57 large cohort studies; after addressing biases, increased mortality was found in overweight and all obese groups in both studies.[2,3] In addition to studies of mortality, which typically occurs at the end of a long process, guidance about weight should also consider the large literature documenting strong relationships between overweight and obesity and incidence of many chronic diseases including hypertension, diabetes, heart disease, stroke, and certain types of cancer.[4]

Indicators of adiposity other than BMI, including abdominal circumference and weight gain, should also be incorporated. Contrary to the conclusions of Flegal et al, the literature provides clear evidence that even modest excess adiposity has many adverse health and social consequences, including lower quality of life, higher health care costs, and elevated mortality.[5]

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In Reply: The goal of our study was neither to endorse nor to criticize the standard BMI categories developed by the World Health Organization, but rather to summarize the published findings on mortality from studies that used those widely recognized categories.

As Dr Viña and colleagues point out, these are categories of weight and not body composition. Our purpose was to present summary estimates that, as we stated, "may help to inform decision making in the clinical setting," a view we believe is reinforced by the Editorial by Heymsfield and Cefalu.[1]

In response to Dr Doehner, the reason that we did not attempt to provide separate estimates for BMI categories of 35 to less than 40 and of 40 or greater was that only 4 studies in our analysis presented those categories separately.

Mr Ramos-Esquivel discusses the possible advantage of the τ^2 statistic over the I^2 statistic. We repeated our sensitivity analysis based on the sequential approach using τ^2 instead of I^2. The results did not change.

Drs Abhyankar and McDonald remind readers that our findings are consistent with other past work, notably that of the late Reubin Andres, MD, a pioneer in this area.

In response to the comments by Dr Willett and colleagues, the inclusion of studies from Asian populations had little effect on our results. We found summary hazard ratios (HRs) for overweight of 0.92 (95% CI, 0.88-0.96) for studies in North American populations and 0.96 (95% CI, 0.92-1.00) for studies in European populations.

Studies that included primarily participants younger than 65 years could not always be separately identified as such. However, for HRs that were clearly only for those younger than 65 years, we found a summary HR of 0.98 (95% CI, 0.94-1.03) for overweight based on 34 HRs, and a summary HR of 1.31 (95% CI, 1.20-1.43) for obesity based on 25 HRs.

Almost all the HRs summarized in our review had been adjusted in the original studies for smoking behavior, clinical conditions, and age, and many studies deleted the first few years of follow-up to minimize possible effects of illness-related weight loss. Thus we believe that almost all the studies in our review were adequately adjusted for these possible confounding factors.

In general, there is little evidence that illness-related weight loss is an important source of bias in these types of studies.[2] Seriously ill people who have lost large amounts of weight and are at high risk of dying may not be likely to participate in population studies.

Willett and colleagues cite a pooled study[3] that showed increased mortality in the overweight group. The investigators in that study deleted almost 900 000 individuals, the majority of the original 1.46 million participants, before arriving at their final results, arguing that it was necessary to exclude persons who had ever smoked and those with a history of heart disease or cancer.

As noted in our article, adding the final results of that study to our analyses did not change our summary HR for overweight. Also noted in our article, many studies in our review found that deletions for smoking and preexisting illness had almost no effect on their results.

We previously showed[4] that deletions for smoking and preexisting illness applied to national survey data resulted in findings that became more strongly negative for the overweight category and less positive for the obesity category, the opposite of the effects hypothesized by Willett and colleagues. The validity of results obtained after large-scale deletions to adjust for confounding by smoking or preexisting illness has not been demonstrated.

Our findings suggest that self-reported weight and height contribute more to bias than do smoking and preexisting illness.

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Disclaimer: The findings and conclusions in this report are those of the authors and not necessarily the official views of the Centers for Disease Control and Prevention or the National Cancer Institute.

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Mega-Randomized Clinical Trials for Blockbuster Drugs

To the Editor: Many commonly used medications lack information regarding their adverse effects, effectiveness relative to other treatment options, and mortality benefits. In his Viewpoint, Dr Ioannidis[1] suggested requiring pharmaceutical companies to fund mega-randomized clinical trials (RCTs) for medications with more than $1 billion in annual sales, using as an example a trial with 20 000 patients, 4 years of follow-up, and mortality as an outcome.

This plan draws on several popular themes such as limiting or redistributing excessive pharmaceutical company profits, relying on experimental design for causal inference, and using objective end points. We believe this plan lacks feasibility, and its anticipated value is unlikely to justify its expense.

This proposal's feasibility rests on conducting RCTs at a 90% discount to current costs. This estimate is derived from a data simulation study of expert recommendations for government-conducted RCTs that did not specify drug costs.[2] Following up 20 000 patients for 4 years using $42 million, as proposed, provides just $525 per patient-year.

Unless pharmaceutical companies are required to donate medications, this budget would not cover the medication costs, which would be $84 million assuming a minimal drug cost of $3 per day. Regardless of ultimate RCT costs, pharmaceutical companies would likely pass these costs onto payers, further increasing health care expenditures.

The proposed method may also fail to generate sufficient value for many blockbuster medications. Given their established efficacy, it is unlikely that RCTs of these medications could ethically include placebo controls. This would diminish their ability to detect adverse effects because active comparators will have their own complications.

Furthermore, active comparator RCTs could either report equivalence given intraclass medication similarities or statistically significant but clinically insignificant effects due to excessive statistical power. Mortality would be irrelevant for nearly two-thirds of the suggested medications that address non–mortality-related problems, such as arthritis, erectile dysfunction, and pain.

Recent initiatives are already addressing many of the issues underlying this proposal. In 2007, the ability of the US Food and Drug Administration to require pharmaceutical companies to conduct postapproval monitoring and remove approved drugs from the market was strengthened.[3] In 2008, the Food and Drug Administration launched the Sentinel Initiative to improve drug safety surveillance.[4] In 2009, the US government allocated $1.1 billion for comparative effectiveness research.[5] In 2010, the US government created the Patient-Centered Outcomes Research Institute to study clinically important outcomes.[5]