Weight and Mortality

To the Editor:

In a recent article, Dr. Hu states¹ that the findings regarding weight and mortality in Flegal et al² are “most likely” the result of “methodologic flaws,” namely the failure to exclude subjects on the basis of smoking and preexisting illness. In August 2005, we replied³ to a similar assertion by Willett, Hu, and colleagues.⁴ In that reply we stated, “To determine if reverse causation might be affecting our results, we performed extensive supplemental analyses of our data, stratifying by baseline health status and using multiple simultaneous exclusions for smoking, early deaths, and involuntary weight loss.²” The relative risks were little affected by such exclusions, and changes were often in the direction opposite to those anticipated by Willett et al.³ Reference 2 in our reply provided the hyperlink to these supplemental analyses: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/excess_deaths/excess_deaths.htm.

Exclusions based on health status, smoking, early deaths, and involuntary weight loss eliminated 80% to 90% of the deaths and made the estimates of relative risks less precise, as has also been seen in other published analyses.³ However, our estimates of excess deaths depend on the point estimates of relative risks, not on their variance (which is taken into account in our standard error calculations). Our supplemental analyses provided no indication that residual confounding by smoking or by preexisting illness biased our results or that our findings on weight and mortality were due to “methodologic flaws.” We encourage interested readers to review these supplemental analyses, which answer the criticisms mentioned by Dr. Hu¹ and greatly expand on the sensitivity analyses.²

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Response

Although the detrimental effects of obesity on incidence of chronic diseases such as cardiovascular disease and cancer are well accepted, the relationship between obesity and mortality remains controversial. A major challenge in analyzing the obesity–mortality association in epidemiological studies is the phenomenon of “reverse causation,” or the fact that low body weight results from chronic disease rather than the opposite. This problem is exacerbated among the elderly because weight loss caused by chronic disease and loss of muscle is common in older age groups. In addition, smokers tend to be leaner but have increased mortality. Although there is no perfect solution to these problems, the best estimates of impact of overweight and obesity should derive from studies with very large sample size and long duration of follow-up, ideally, beginning in midlife or earlier.

Although Flegal and colleagues conducted secondary analyses, such as excluding persons with a history of weight loss, smokers, and perceived health status, it is not clear whether such analyses can adequately address the problem of reverse causation considering that participants with chronic diseases at baseline were not explicitly excluded and that a large number of the deaths in National Health and Nutrition Examination Survey occurred among people aged 70 or older at the time of body mass index (BMI) assessment. Also, the follow-up periods for National Health and Nutrition Examination Survey II and III were relatively short; reverse causation is more likely to have a greater impact in the early years of follow-up. The estimates provided in supplementary analyses posted on the web appear to be highly unstable, probably because of the small number of deaths. Unfortunately, the researchers did not provide either the number of deaths for the subgroups or confidence intervals surrounding the estimates. As shown in Flegal et al.,¹ estimates of the number of deaths attributable to obesity are extremely sensitive to even small changes in relative risk estimates.

Several large cohort studies that have assessed BMI in midlife (in ages 40s, 50s, and 60s) show that overweight and obesity significantly predict an increased risk of total and cardiovascular death over the subsequent decades.²–⁴ For example, in the updated analyses of 116 564 women aged 30 to 55 in the Nurses’ Health Study with 24 years of follow-up,² we found that baseline BMI was a strong predictor of mortality in the overall cohort and as expected, the association was substantially stronger among those who never smoked. Thus, epidemiologic studies with very large sample sizes of healthy participants and long durations of follow-up are needed to conduct comprehensive analyses of obesity and mortality that can adequately address threat to internal validity resulting from reverse causation. Such studies are directly relevant to public health and prevention rather than simply statistical predictions.

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