No hazard or better health from weight loss?1,2

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The investigators of the Trial of Nonpharmacologic Intervention in the Elderly (TONE) have attempted to test whether there is an adverse effect of weight loss, ie, increased mortality (1). This approach is similar to trying to determine whether a specific drug therapy in a clinical trial increases mortality and morbidity, especially in a selected subset of the population. Unfortunately, there remains no solid evidence from clinical trials that weight loss reduces total mortality or cause-specific mortality, ie, cardiovascular disease (CVD). An obesity pseudo-trial reported after 12 y of follow-up a reduction in total mortality following substantial weight loss after bariatric surgery (2). This reduction in mortality was primarily due to cancer and not to CVD.

Weight-loss trials, such as the TONE, have 3 major weaknesses that dramatically limit their interpretation with regard to the hypothesis that weight loss will reduce morbidity and mortality. First, the amount of weight loss is very small, especially in the long term, ie, an average of 5% weight loss over 30–36 mo (3, 4). Second, the length of the intervention and active follow-up is often too short. Many of the individuals in these trials regain the weight over time. Thus, there is a component of weight regain to consider as well as weight loss early in the trial. For example, maybe women in the TONE who lost a fair amount of weight initially regained more weight during the follow-up, and this resulted in their reported increased mortality (1). Third, behavioral intervention trials are obviously unblinded. The change in other behaviors (eg, adherence to drug therapy, use of other drugs, or use of other alternative therapies) in both the intervention and comparison groups can have profound effects on the interpretation of the results of this study. This is especially important in the era of the widespread use of lipid-lowering therapies, statins, antihypertensive therapy, and similar treatments.

Adverse effects in a clinical trial often require a much larger sample size than that needed to prove the primary hypothesis of a specific benefit. With the assumption that weight loss has no overall benefit but is likely to have an adverse effect in a subsample of 20% of the individuals in the study—ie, an increase of 50% of the mortality—then the overall adverse effect in the trial would only be ~10% (ie, 50% in the 20% at risk). Such a result would be within the confidence limits of the main effects of the TONE. If weight loss was being treated like a drug effect, would the observed increase in mortality among women require a black box warning on all weight-loss programs for women? This is highly unlikely.

Unfortunately, after many years and numerous behavioral weight-loss trials, we still do not have an effective approach to maximizing substantial weight loss except for surgery (5–8). It is therefore very difficult to test in a randomized trial the potential benefit of weight loss on reducing CVD or total mortality. It is sad that the best results of a weight-loss trial are that it did not increase mortality. The important question from the TONE and other weight-loss behavioral trials is whether the focus of the benefits of weight loss should be shifted to decreasing disability and improving physical function as primary endpoints and less on reduction of CVD and total mortality, especially in middle-aged and older individuals (9, 10).

The investigators of the TONE should be congratulated in continuing the long-term follow-up of this weight-loss study. The long-term follow-up in trials may provide important new results (4). Follow-up of many behavioral clinical trials is not given a high priority. Weight loss, exercise, or both have a benefit in reducing lower extremity functional disability. The TONE provides limited support for the safety of weight-loss programs to reduce disability in older individuals.

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REFERENCES

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