The effect of intentional weight loss on all-cause mortality in older adults: results of a randomized controlled weight-loss trial1–3


ABSTRACT

Background: Despite the reported benefits, weight loss is not always advised for older adults because some observational studies have associated weight loss with increased mortality. However, the distinction between intentional and unintentional weight loss is difficult to make in an observational context, so the effect of intentional weight loss on mortality may be clarified in the setting of a randomized controlled trial.

Objective: The objective was to determine the effect of intentional weight loss on all-cause mortality by using follow-up data from a randomized trial completed in 1995 that included a weight-loss arm.

Design: The Trial of Nonpharmacologic Intervention in the Elderly (TONE) used a 2 × 2 factorial design to determine the effect of dietary weight loss, sodium restriction, or both on blood pressure control in 585 overweight or obese older adults being treated for hypertension (mean ± SD age: 66 ± 4 y; 53% female). All-cause mortality was ascertained by using the Social Security Index and National Death Index through 2006.

Results: The mortality rate of those who were randomly assigned to the weight-loss intervention (n = 291; mean weight loss: 4.4 kg) did not differ significantly from that of those who were not randomly assigned to this group (n = 294; mean weight loss: 0.8 kg). The adjusted HR was 0.82 (95% CI: 0.55, 1.22).

Conclusions: Intentional dietary weight loss was not significantly associated with increased all-cause mortality over 12 y of follow-up in older overweight or obese adults. Additional studies are needed to confirm and extend our findings to older age groups. This trial is registered at clinicaltrials.gov as NCT00000535. Am J Clin Nutr 2011;94:839–46.

INTRODUCTION

Randomized trials of moderate weight loss show that older adults who lose weight can improve their overall health and quality of life, including improvements in several age-related morbidities and physical function (1–4). It would follow that weight loss may also reduce mortality risk, but many observational studies have associated weight loss with an increased risk of mortality (5–7). Therefore, controversy exists as to whether weight loss should be recommended for older overweight/obese adults (8). Considering the increasing prevalence of overweight and obesity in older men and women and the strong association of obesity with functional limitation, it is important to know the benefits and risks of weight loss in the older segment of the population.

The discrepancy between the observational studies and intervention studies may stem from the discrimination of intentional from unintentional weight loss. Unintentional weight loss can indicate underlying subclinical but serious disease, which would increase mortality risk and may explain some of the observational data. It has been suggested that analyses of randomized controlled weight-loss trials are needed to fully understand the effect of intentional weight loss on mortality (9). We recently compared the mortality rates of 318 older overweight and obese adults with knee osteoarthritis who were either randomly assigned to an 18-mo weight-loss intervention or a control group. After 8 y of follow-up, the total (all-cause) mortality rate was 50% lower in those randomly assigned to the weight-loss intervention (10). Because this was the first known study to examine the effect of intentional weight loss on all-cause mortality using a randomized controlled study design, this finding merits confirmation in other weight-loss intervention trials and in populations with different comorbidities.

Accordingly, the goal of the current analysis was to determine the effect of intentional weight loss on all-cause mortality in the TONE.4 TONE was a randomized controlled intervention trial designed to determine the efficacy of dietary weight loss and sodium reduction, alone or in combination, on the maintenance of blood pressure control after withdrawal of antihypertensive

1 From the Department of Internal Medicine, Section on Gerontology and Geriatric Medicine (MKS, BJN, DKH, DWK, and SBK), Division of Public Health Sciences (MEM, CCD, and MAE), Department of Internal Medicine, Section on Cardiology (DWK), Wake Forest University School of Medicine, Winston-Salem, NC, and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD (LJA).
2 Supported by the National Institutes of Aging (RO1 AG09799, RO1 AG09771, and RO1 AG09773); the National Heart, Lung, and Blood Institute (RO1 HL48642); and the Wake Forest University School of Medicine Claude Pepper Center (P30 AG21332).
3 Address correspondence to SB Kritchevsky, Sticht Center on Aging, Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: skritchew@wfubmc.edu.
4 Abbreviations used: ADAPT, Arthritis, Diet and Activity Promotion Trial; CVD, cardiovascular disease; DBP, diastolic blood pressure; NDI, National Death Index; SBP, systolic blood pressure; SSI, Social Security Index; T2DM, type 2 diabetes; TONE, Trial of Nonpharmacologic Intervention in the Elderly.

Received October 15, 2010. Accepted for publication June 1, 2011. First published online July 20, 2011; doi: 10.3945/ajcn.110.006379.
medications in older men and women (3). We analyzed mor-
tality data from the 585 older overweight and obese men and
women previously treated for hypertension who were randomly
assigned to a weight-loss intervention trial or a non–weight-loss
intervention over 12 y of follow-up.

SUBJECTS AND METHODS

Participants

The primary goal of the main TONE was to determine whether
dietary weight loss and/or sodium restriction were effective at
treating hypertension. The design and primary outcome of TONE
were previously described in detail (3). Participants were re-
cruited to 4 field centers and randomly assigned to 1 of 4
treatment groups: dietary weight loss, sodium reduction, dietary
weight loss + sodium reduction, or usual lifestyle control. At
enrollment (1992–1994), participants had systolic and diastolic
blood pressures of <145 and <85 mm Hg, respectively, and
were taking a single hypertensive medication or a single com-
bination therapy of one diuretic and one non-diuretic agent.
Exclusion criteria included history of heart attack or stroke
within the previous 6 mo, current angina or congestive heart
failure, atrial fibrillation, insulin-dependent diabetes, unex-
plained weight loss of ≥4.5 kg within the past year, diagnosis or
treatment of cancer within the past 5 y, treatment of asthma or
obstructive pulmonary disease within the previous 6 mo, and
inability to walk one block or climb one flight of stairs (3).
TONE enrolled a total of 975 men and women, 585 of whom
were overweight or obese and were eligible to be randomly
assigned to the dietary weight-loss intervention. Those who were
not overweight/obese were not eligible to be randomly assigned
to the weight-loss intervention; 585 overweight/obese persons
were included in the current analysis. All TONE participants
provided written informed consent. TONE was approved by the
institutional review boards at the 4 field centers (Wake Forest
University School of Medicine, Johns Hopkins University
School of Medicine, Robert Wood Johnson Medical School, and
University of Tennessee at Memphis).

Interventions

The dietary weight-loss and sodium reduction interventions
are detailed elsewhere (3). The weight-loss intervention was
designed to achieve and maintain a 4.5-kg weight loss, and the
sodium-reduction intervention was designed to maintain a so-
dium intake of ≤1800 mg/d. Both interventions were supervised
behavior-based and consisted of 3 phases: 1) a 4-mo intensive
phase that provided participants with training and behavior-
based counseling to lose weight or reduce sodium intake; 2) a
4-mo extended phase, which focused on problem solving and
maintenance of weight loss or sodium reduction; and 3) a
maintenance phase, during which repeated attempts were
made to maintain participant interest and reengage those who
were less active in phase 2 until close-out, which occurred an
average of 28 mo (range: 16–36 mo) after enrollment. Trained
nutritionists and exercise counselors advised participants on
changing eating behaviors and increasing physical activity.
Walking was the most recommended form of exercise (11). The
usual lifestyle control group received no study-related counsel-

Data collection

Death ascertainment

Death determination was completed without knowledge of
randomization group by trained personnel who were not involved
in the original trial. Deaths during follow-up were ascertained by
using the SSI and the NDI; the specificity and sensitivity of the
NDI are better than those of the SSI (12). The agreement in death
ascertainment between the 2 databases was reported to be >94%
when identification information similar to what was available in
our study was used (13). At the time of ascertainment, NDI data
were available through 31 December 2006, which was used as
the censoring date for all analyses. No attempt was made to
identify cause of death.

Covariates

SBP and DBP were measured at baseline in triplicate. At the
same time, weight and height (without shoes) were measured by
using the same calibrated scale. BMI was calculated as weight
(kg)/height squared (m). Demographic information and medical
history (including medication use) was collected at baseline, and
medical history was reevaluated at each follow-up visit.

Statistical analyses

Because our primary purpose was to determine the effect of
intentional weight loss on all-cause mortality, the dietary weight
loss and dietary weight loss + sodium-reduction groups were
combined as the weight-loss-intervention group. Those in the
sodium-reduction-only and in the usual-lifestyle control groups
were combined as the non–weight-loss-intervention group. The
weight-loss and non–weight-loss groups were compared at baseline
by using Student’s t test (2-tailed) for independent samples, and
the chi-square test was used for differences in proportions,
for continuous and categorical outcomes, respectively. For the
current analyses, weight loss was calculated from data obtained
during the 9-mo and 18-mo follow-up visits. The all-cause
mortality rate in the 2 study groups was compared by using
Cox proportional hazards regression. The intent-to-treat un-
adjusted analysis included all 585 participants, and the data are
presented as HRs and 95% CIs. Subsequent analyses were ad-
justed for age, sex, race, study site, smoking status, DBP, history
of CVD, and randomization to sodium reduction. These analy-
ases included 291 participants randomly assigned to a non–
weight-loss group and 294 participants randomly assigned to
a weight-loss-intervention group (Figure 1). To determine the
consistency of the effect of intentional weight loss on all-cause
mortality, we stratified the analyses by sex, race, and age (≤65 y,
the median age at baseline, and >65 y). All stratifications were
prespecified according to previous studies (10, 11). Given the
analysis of 6 subgroups, the probability of type 1 error from
testing 6 null hypotheses was 0.265, assuming independence of
the tests. We also compared the mortality of the 4 separate
intervention groups to determine the influence of randomization to sodium reduction on all-cause mortality using Cox proportional hazards regression. The assumption of proportional hazards was evaluated by testing the interaction between the main effects of interest and the log measure of time. None of these interactions were significant, which suggests that the assumption was reasonable.

Because the amount of weight lost may influence mortality risk, we compared the all-cause mortality rates of those who lost more than the median of initial body weight (4.1 kg) to those who lost less than or equal to the median body weight at 18 mo in participants in the weight-loss group and in the non–weight-loss group, separately. Because of missing follow-up data, these analyses included 245 and 259 participants randomly assigned to a non–weight-loss and weight-loss intervention groups, respectively. Person-time was calculated from the date of randomization to the date of death or censoring (31 December 2006).

To examine the totality of the evidence of the effect of intentional weight loss on mortality from randomized trials, we combined the data from TONE with the data from ADAPT, for which we previously reported the effect of intentional weight loss on all-cause mortality (10). Initially, we fit a 3-factor interaction (and all 2-factor interactions) between weight-loss intervention, study, and sex with respect to all-cause mortality. This interaction was not significant ($P = 0.496$), so we dropped it from the model. None of the 2-factor interactions were significant either (all $P > 0.584$). Therefore, we determined the effect of intentional weight loss on all-cause mortality in the combined studies, overall, and in men and women using proportional hazards regression adjusted for age, sex (for overall model), race, study, and CVD history. The mean follow-up for TONE was >12 y and for ADAPT was 8 y, so for this pooled analysis we used a censoring date that corresponded to 8 y after the first randomization date in TONE. All analyses were carried out by using SAS 9.1 (SAS Institute Inc, Cary, NC), and the results were considered statistically significant if $P < 0.05$.

RESULTS

The baseline characteristics of the weight-loss and non–weight-loss groups are presented overall and for men and women separately in Table 1. Overall, the mean ± SD age was 65.5 ± 4.5 y and the mean ± SD BMI (in kg/m$^2$) was 31.1 ± 2.3. The weight-loss-intervention group had fewer women than did the non–weight-loss group (47% compared with 57%). Women who were randomly assigned to a non–weight-loss intervention had a higher diastolic blood pressure than did women randomly assigned to the weight-loss intervention (71.1 ± 7.5 compared with 68.5 ± 9.8 mm Hg). Participants in the weight-loss group lost significantly more weight than did the non–weight-loss group at 9 and 18 mo of follow-up (Table 2). The mean overall follow-up time was 12.7 ± 2.4 y and was similar in the 2 groups.

There were no deaths during the TONE intervention phase (3). Over 12 y of follow-up, 101 TONE participants died. Six deaths occurred within the first 2 y of follow-up: 2 in the weight-loss group and 4 in the non–weight-loss group. Overall, the mortality

TABLE 1
Baseline characteristics of participants in the Trial of Nonpharmacologic Intervention in the Elderly (TONE) according to weight-loss intervention

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight loss</td>
<td>Non–weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Female (%)</td>
<td>47</td>
<td>57</td>
<td>NA</td>
</tr>
<tr>
<td>White (%)</td>
<td>75</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.5 ± 10.7&lt;sup&gt;2&lt;/sup&gt;</td>
<td>87.0 ± 10.0</td>
<td>93.6 ± 9.6</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>31.2 ± 2.2</td>
<td>31.1 ± 2.4</td>
<td>30.6 ± 1.6</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>128.1 ± 11.5</td>
<td>127.5 ± 12.3</td>
<td>128.4 ± 11.3</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71.0 ± 9.2</td>
<td>71.8 ± 7.7</td>
<td>73.2 ± 8.1</td>
</tr>
<tr>
<td>Duration of antihypertensive medication treatment (y)</td>
<td>11.0 ± 9.9</td>
<td>11.1 ± 10.1</td>
<td>9.9 ± 8.4</td>
</tr>
</tbody>
</table>

<sup>1</sup> NA, not applicable.
<sup>2</sup> Mean ± SD (all such values).
<sup>3</sup> Significantly different from weight loss, P = 0.01 (Student’s t test).

The effect of intentional weight loss on all-cause mortality did not differ significantly by race (P = 0.56) or age (P = 0.79) (Table 4). However, men who were randomly assigned to the weight-loss group had a significantly lower mortality rate than did men who were not (HR: 0.52; 95% CI: 0.30, 0.91; P-sex × intervention interaction = 0.006). The difference in all-cause mortality between women randomly and not randomly assigned to the weight-loss group was not significant (HR: 1.47; 95% CI: 0.82, 2.65). Given the coverage of the 95% CI, harm associated with weight loss in the women in TONE was plausible.

Among participants randomly assigned to the weight-loss-intervention group, the total mortality rate of participants who lost more than the median body weight (4.1 kg) was not significantly different from those who lost less than or equal to the median body weight at 18 mo of follow-up (HR: 1.50; 95% CI: 0.78, 2.87; P = 0.22). However, among participants randomly assigned to the non–weight-loss intervention, those who lost >4.1 kg had a mortality rate >2.5-fold that of those who lost ≤4.1 kg (HR: 2.58; 95% CI: 1.18, 5.65).

Because TONE and ADAPT participants shared common characteristics, including a similar behavior-based weight-loss intervention and a similar amount of weight lost over 18 mo, with only overweight/obese participants aged ≥60 y at baseline (1, 3), we combined the data from both studies, which provided >900 participants, and the results confirmed that randomization to dietary weight loss results in little or no increase in all-cause mortality (Figure 3).

DISCUSSION

After 12 y of follow-up, no significant difference overall was found in all-cause mortality between older overweight and obese adults who were randomly assigned to an intentional weight-loss intervention and those who were not. To our knowledge this was the second report of the effect of randomization to intentional weight loss on total mortality. In our previous report—a similar analysis of older men and women with knee osteoarthritis who participated in ADAPT, an 18-mo weight-loss intervention—those randomly assigned to a weight-loss intervention had a 50% lower mortality rate over 8 y of follow-up (HR: 0.5; 95% CI: 0.3, 0.9) (10). TONE does not confirm a large benefit of intentional weight loss with respect to reducing all-cause mortality in older age. However, our results also do not implicate intentional weight loss to be significantly associated with an increased mortality risk, as suggested by several observational studies (5–7). However, the results will be strengthened by including additional data from other weight-loss-intervention trials in the future.

To date, the association between weight loss and mortality has been primarily studied observationally, with inconsistent results. Of the observational studies that attempted to stratify according

TABLE 2
Weight change in participants in the Trial of Nonpharmacologic Intervention in the Elderly (TONE) by weight-loss and non–weight-loss interventions at 9 and 18 mo of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight loss</td>
<td>Non–weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>9 mo (kg)</td>
<td>−5.0 ± 4.5 (274)</td>
<td>−1.1 ± 3.4 (260)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>18 mo (kg)</td>
<td>−4.4 ± 4.8 (259)</td>
<td>−0.8 ± 3.7 (245)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<sup>1</sup> All values are means ± SDs. n in parentheses.
to weight-loss intent, the association between intentional weight loss and mortality remains unclear. As reviewed elsewhere (14), in overweight but otherwise healthy men and women, intentional weight loss of 2 to 5 kg has been associated with a 1.3–1.9-fold increased risk of mortality by some (6, 7, 15), whereas others have indicated that an intentional weight loss of 3 to 7 kg is associated with a 0.6–0.7-fold reduction in the mortality rate (16, 17). Other studies, including a meta-analysis that combined data from all available observational studies through 2008, reported no significant association between intentional weight loss and all-cause mortality (5, 18, 19). Despite the attempts to do so, it has been suggested that weight loss intent cannot be accurately determined in observational studies, and randomized controlled weight-loss trials are more appropriate for addressing this question, because the observed weight loss would be expected to be intentional and randomization would resolve any confounding influence by subclinical disease (20).

In contrast with ADAPT (10), the stratified analyses of TONE unexpectedly found that the effect of intentional weight loss on all-cause mortality differed between men and women. Although the basis for this finding is uncertain and no plausible hypothesis for this observation is able to be addressed with the available data, it may be attributable to one or a combination of the following 1) our results reflect sampling variability, 2) there was an unknown difference in death ascertainment between men and women (ascertainment bias), 3) randomization did not balance the health status across intervention groups in one sex as well as the other, 4) the posttrial experiences differed by sex, or 5)

![FIGURE 2. Cumulative all-cause mortality associated with randomization to dietary weight loss in the Trial of Nonpharmacologic Intervention in the Elderly (TONE). Based on Cox proportional hazards regression.](image)

### TABLE 3

Total mortality in participants in the Trial of Nonpharmacologic Intervention in the Elderly (TONE) by randomly assigned group

<table>
<thead>
<tr>
<th>Group-specific results</th>
<th>No. of subjects</th>
<th>Person-years</th>
<th>No. of deaths (n = 101)</th>
<th>Death rate (per 100 person-years)</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No–weight-loss intervention</td>
<td>Non–weight-loss intervention</td>
<td>294</td>
<td>3708.3</td>
<td>52</td>
<td>1.4</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Weight-loss intervention</td>
<td>291</td>
<td>3769.1</td>
<td>49</td>
<td>1.3</td>
<td>0.93 (0.63, 1.37)</td>
<td>0.70</td>
<td>0.82 (0.55, 1.22)</td>
<td>0.32</td>
</tr>
<tr>
<td>Non–sodium-reduction intervention</td>
<td>291</td>
<td>3768.5</td>
<td>50</td>
<td>1.3</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium-reduction intervention</td>
<td>294</td>
<td>3708.9</td>
<td>51</td>
<td>1.4</td>
<td>1.04 (0.70, 1.53)</td>
<td>0.85</td>
<td>1.04 (0.70, 1.54)</td>
<td>0.86</td>
</tr>
<tr>
<td>Group-specific results</td>
<td>Control</td>
<td>147</td>
<td>1872.2</td>
<td>28</td>
<td>1.5</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Weight loss only</td>
<td>147</td>
<td>1896.3</td>
<td>22</td>
<td>1.2</td>
<td>0.78 (0.44, 1.36)</td>
<td>0.37</td>
<td>0.68 (0.39, 1.20)</td>
<td>0.19</td>
</tr>
<tr>
<td>Sodium reduction</td>
<td>144</td>
<td>1836.1</td>
<td>24</td>
<td>1.3</td>
<td>0.88 (0.51, 1.51)</td>
<td>0.63</td>
<td>0.87 (0.50, 1.51)</td>
<td>0.62</td>
</tr>
<tr>
<td>Sodium reduction + weight loss</td>
<td>147</td>
<td>1872.8</td>
<td>27</td>
<td>1.4</td>
<td>0.96 (0.57, 1.64)</td>
<td>0.89</td>
<td>0.85 (0.50, 1.46)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

1 Based on Cox proportional hazards regression.

2 Adjusted for age, sex, race, study site, smoking status, diastolic blood pressure, history of cardiovascular disease, and random assignment to sodium reduction.

3 Adjusted for age, sex, race, study site, smoking status, diastolic blood pressure, history of cardiovascular disease, and random assignment to dietary weight loss.
intentional weight loss is indeed beneficial for older men and not for older women. Death status was determined without knowledge of the randomized group, so ascertainment bias was unlikely. With the exception of a slight but significant increase in DBP in women in the non–weight-loss group, the potential confounders (including age, smoking status, BMI, duration of antihypertensive medication use, and history of CVD) appeared to be balanced between the weight-loss and non–weight-loss groups. In addition, no differences in the self-reported overall health status of men and women in the weight loss and non–weight-loss interventions at baseline were found (data not shown). Before enrollment in TONE, the women had been treated with hypertension medication longer than had the men, and the treatment regimens differed between the women and men (21). During TONE, there was no evidence that withdrawal of medication to treat hypertension, TONE participants in the weight-loss groups were significantly less likely to become hypertensive (HR: 0.70; 95% CI: 0.57, 0.87) (3). Results of the Diabetes Prevention Program found that participation in a lifestyle modification intervention (focused on weight loss through behavior modification) was more beneficial to older men and women (60–85 y) than to younger men and women in preventing T2DM over an average 3.2 y of follow-up (24). Participants in the lifestyle modification intervention lost 4 kg (on average) and had a 58% lower incidence of T2DM overall. Among participants aged ≥60 y, the incidence of T2DM in the lifestyle intervention group was reduced by 70% (4). The results of a recent dietary intervention study found that a 3–5-kg weight loss was associated with a significant regression in carotid wall volume over 2 y, which is reflective of an improvement in subclinical atherosclerosis (25). These studies provide a basis to expect that intentional weight loss may be helpful to older adults, mortality concerns notwithstanding. However, the effect of intentional weight loss on age-related comorbidities and mortality has focused primarily on the “young-old.” Populations aged >70 y have not been well studied and merit future investigation.

We also examined the association between the magnitude of weight loss and all-cause mortality in both the weight-loss and non–weight-loss intervention groups. Among participants randomly assigned to a non–weight-loss intervention, those who lost the most weight had a >2.5-fold higher mortality rate than those who lost less. Intention was not ascertained in TONE, and the weight loss in this group was likely to have been a mix of intentional and unintentional weight loss. It is interesting that this nonrandomized group showed an association typical of other observational weight-loss studies (6, 18, 26–28). Exclusion of participants with missing follow-up weights (16% in the non–weight-loss group, 12% in the weight-loss group) may have introduced bias to this secondary analysis. Randomization to a low-sodium diet was not significantly associated with total

### TABLE 4

<table>
<thead>
<tr>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>No. of subjects</th>
<th>Person-years</th>
<th>No. of deaths</th>
<th>Death rate (per 100 person-years)</th>
<th>HR (95% CI)</th>
<th>( P )</th>
<th>Adjusted HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Non–weight loss</td>
<td>124</td>
<td>1531.6</td>
<td>31</td>
<td>2.0</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>155</td>
<td>1998.8</td>
<td>23</td>
<td>1.2</td>
<td>0.56 (0.33, 0.96)</td>
<td>0.03</td>
<td>0.52 (0.30, 0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non–weight loss</td>
<td>167</td>
<td>2176.7</td>
<td>21</td>
<td>1.0</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>139</td>
<td>1770.3</td>
<td>26</td>
<td>1.5</td>
<td>1.54 (0.87, 2.75)</td>
<td>0.14</td>
<td>1.47 (0.82, 2.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>Non–weight loss</td>
<td>90</td>
<td>1153.1</td>
<td>14</td>
<td>1.2</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>74</td>
<td>949.9</td>
<td>8</td>
<td>0.8</td>
<td>0.69 (0.29, 1.64)</td>
<td>0.40</td>
<td>0.55 (0.22, 1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non–weight loss</td>
<td>201</td>
<td>2555.2</td>
<td>38</td>
<td>1.5</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>220</td>
<td>2819.2</td>
<td>41</td>
<td>1.5</td>
<td>0.98 (0.63, 1.52)</td>
<td>0.91</td>
<td>0.86 (0.55, 1.36)</td>
</tr>
<tr>
<td>≤65 y</td>
<td>Black</td>
<td>Men</td>
<td>Non–weight loss</td>
<td>182</td>
<td>2366.4</td>
<td>25</td>
<td>1.1</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≤65 y</td>
<td>White</td>
<td></td>
<td>Weight loss</td>
<td>164</td>
<td>2158.6</td>
<td>19</td>
<td>0.9</td>
<td>0.83 (0.46, 1.50)</td>
<td>0.53</td>
<td>0.79 (0.44, 1.44)</td>
</tr>
<tr>
<td>&gt;65 y</td>
<td>Non–weight loss</td>
<td>109</td>
<td>1341.9</td>
<td>27</td>
<td>2.0</td>
<td></td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 y</td>
<td>Weight loss</td>
<td>130</td>
<td>1610.5</td>
<td>30</td>
<td>1.9</td>
<td></td>
<td>0.93 (0.55, 1.56)</td>
<td>0.78</td>
<td>0.95 (0.56, 1.61)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

1 Based on Cox proportional hazards regression.
2 Adjusted for age, sex, race, site, smoking, diastolic blood pressure, and sodium reduction intervention (unless stratified on that variable).
mortality in the TONE participants. In a younger population (35–54 y), Cook et al (29) reported that prehypertensive adults randomly assigned to dietary sodium reduction had a lower risk of all-cause mortality over 10–15 y of follow-up in the Trials of Hypertension Prevention. However, the reduction was not significant (relative risk: 0.80; 95% CI: 0.51, 1.26; \(P = 0.34\)) and our point estimate is contained within the 95% CI they report.

Several limitations of our analysis should be kept in mind: TONE was not designed to test the effect of weight loss on total mortality. At the time of enrollment, the TONE participants were primarily 60–70 y of age. They were being treated for hypertension but were otherwise healthy, because most other significant comorbidities were exclusions (30), and the amount of weight lost was modest (5% of initial body weight). Thus, our ability to generalize our findings to adults aged >70 y, to less healthy populations, or to persons losing greater amounts of weight was limited. Overall the 12-y mortality rate in TONE was low (17.7% in the non-weight-loss group and 16.8% in the weight-loss group), which may have been due, in part, to the overall health of TONE participants. The low event rates reduced our precision in estimating the difference between groups. The upper bound of the adjusted 95% CI in TONE rules out that randomization to weight loss increases mortality risk by >22%, and the combined results of TONE and ADAPT rule out that randomization to weight loss increases mortality risk (upper 95% CI: 0.98). Cause-specific mortality was not available in the current study, and it is possible that intentional weight loss may affect cardiovascular mortality differently in hypertensive adults. Information on the health and/or lifestyle of TONE participants after completion of TONE (in 1995) was not available. It is possible that mortality was affected by posttrial behaviors. Unfortunately posttrial behavioral data were not available. Our examination of the effect of weight loss on mortality according to weight-loss experience (stratified as greater than or less than or equal to the median weight loss) did not include participants who were missing 18-mo follow-up data. This “missingness” may not have been random because 1) those without follow-up data may not have completed the study because of illness, and 2) participants’ randomly assigned to weight loss who did not lose weight may have been less likely to complete the study. However, all other analyses were intent-to-treat and thus were not susceptible to the same bias.

In conclusion, all-cause mortality did not differ significantly between older overweight/obese adults who were randomly assigned to weight loss and those who were not randomly assigned to this group. The effect of randomization to dietary weight loss on all-cause mortality appeared to be affected by sex, which suggests greater benefit to men than to women. These results combined with those of our previous study indicate that randomization to intentional weight loss does not increase mortality in older persons (60–80 y). Additional research is needed to confirm this and to extend the findings to older age groups.

**FIGURE 3.** The effect of intentional weight loss on all-cause mortality over 8 y of follow-up in participants in the Trial of Nonpharmacologic Intervention in the Elderly (TONE); in the Arthritis, Diet, and Activity Promotion Trial (ADAPT); and in the studies combined. \(^a\)Adjusted for age, sex (unless stratified), race, study site, history of cardiovascular disease (CVD), diastolic blood pressure, smoking status, and random assignment to a low-sodium intervention. \(^b\)Adjusted for age, sex (unless stratified), history of CVD, and random assignment to exercise intervention. \(^c\)Adjusted for age, sex (unless stratified), race, history of CVD, and study (TONE or ADAPT).
The authors’ responsibilities were as follows—MKS, BJN, DKH, and SBK: designed the study; MKS, MAE, and LJA: acquired the data; CCD, MEM, and MAE: analyzed the data; MKS and SBK: drafted the manuscript; and BJN, DKH, DWK, MAE, MEM, LJA, and SBK: provided critical intellectual content for the manuscript revision. No conflicts of interest were reported.

REFERENCES


