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Association of Later-Life Weight Changes With Survival to Ages 90, 95, and 100: The Women's Health Initiative

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Abstract

Background: Associations of weight changes and intentionality of weight loss with longevity are not well described.

Methods: Using longitudinal data from the Women's Health Initiative (*N* = 54 437; 61–81 years), we examined associations of weight changes and intentionality of weight loss with survival to ages 90, 95, and 100. Weight was measured at baseline, year 3, and year 10, and participants were classified as having weight loss (≥5% decrease from baseline), weight gain (≥5% increase from baseline), or stable weight (<5% change from baseline). Participants reported intentionality of weight loss at year 3.

Results: A total of 30 647 (56.3%) women survived to ≥90 years. After adjustment for relevant covariates, 3-year weight loss of ≥5% vs stable weight was associated with lower odds of survival to ages 90 (OR, 0.67; 95% CI, 0.64–0.71), 95 (OR, 0.65; 95% CI, 0.60–0.71), and 100 (OR, 0.62; 95% CI, 0.49–0.78). Compared to intentional weight loss, unintentional weight loss was more strongly associated with lower odds of survival to age 90 (OR, 0.83; 95% CI, 0.74–0.94 and OR, 0.49; 95% CI, 0.44–0.55, respectively). Three-year weight gain of ≥5% vs stable weight

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was not associated with survival to age 90, 95, or 100. The pattern of results was similar among normal weight, overweight, and obese women in body mass index (BMI)-stratified analyses.

Conclusions: Weight loss of ≥5% vs stable weight was associated with lower odds of longevity, more strongly for unintentional weight loss than for intentional weight loss. Potential inaccuracy of self-reported intentionality of weight loss and residual confounding were limitations.

Keywords: Longevity, Obesity, Successful aging

Findings on the relationship between weight change and mortality have been inconsistent due, in part, to differences in the ages at which weight changes occurred and the need to consider intentionality of weight loss (1–15). Studies among National Health and Nutrition Examination Survey participants found that moving from nonobese to obese between young and middle adulthood was associated with 22% higher risk of mortality, and that weight loss from obese to overweight was associated with 54% lower risk of mortality (3,13). Weight changes from early to middle adulthood are related to many significant health outcomes, including healthy aging. For example, in the Nurses' Health and Health Professionals Follow-up studies, a moderate amount of weight gain (≥2.5 to <10 kg) from early to middle adulthood was associated with 22% and 12% lower odds of being free of 11 chronic diseases and cognitive and physical impairment later in life in women and men, respectively (15). However, these studies did not consider intentionality of weight loss. Some studies have shown lower mortality rates in adults reporting intentional weight loss, and higher mortality rates in those reporting unintentional weight loss (16,17). Others have reported no associations of intentional weight loss with mortality among adults (17,18).

The association of weight changes with mortality may differ for older adults, given decreases in muscle mass and increases in fat mass that occur with aging (19). Some have found that both weight gain and loss vs stable weight are associated with higher mortality in older adults, whereas others have reported no associations of weight gain with mortality (1,9,10). A study in the Baltimore Longitudinal Study of Aging cohort showed that weight loss accelerated an average of 9 years before death and that weight loss trajectories varied according to cause of death, with weight loss accelerating in the 3 years prior to death from cancer and 5 or more years before death due to cardiovascular disease (20). Yet, to our knowledge, no prior study has determined whether later life weight changes were associated with exceptional longevity. This is due to the existence of few cohorts with large numbers of participants who have been followed long enough to reach exceptional ages.

Therefore, we examined associations of short-term (3-year) and long-term (10-year) weight changes with survival to ages 90, 95, and 100 among older women. We also examined whether intentional and unintentional weight loss differed in their associations with survival to these ages.

Method

Study Participants

The Women's Health Initiative (WHI) is a prospective study investigating major determinants of chronic diseases among postmenopausal women (21). A cohort of 161 808 postmenopausal women ages 50–79 years were recruited during 1993–1998 across 40 U.S. clinical centers into an observational study (OS; N = 93 676) or one or more of 3 clinical trials (CT; N = 68 132), which included 2 hormone therapy trials, a dietary modification trial, and a calcium plus vitamin D supplementation trial.

We examined observational study (OS) and clinical trial (CT) women with weight measured at baseline and year 3 (N = 120 411). We restricted analyses to women born on or before February 19, 1932, with the potential, due to birth year, to survive to age 90 during follow-up ending February 19, 2022, and with complete information on survival status (N = 54 783). After excluding 346 women who died within the first year of the year 3 visit to minimize bias due to reverse causation (eg, due to preexisting illness), the final analytic cohort consisted of 54 437 women (Supplementary Figure 1). Analyses for survival to ages 95 and 100 were restricted to a subset born on or before February 19, 1927 (N = 28 014) and February 19, 1922 (N = 9 050), respectively. This study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Each participant provided written informed consent.

Clinical trial (but not OS) women had weight measured every year from 1993 to 2005. Among these women, we additionally examined weight changes from baseline to the clinic visit approximately 10 years later (± 2 years) among women 69–85 years at year 10, to allow a minimum of 5 years of follow-up to ≥90 years (N = 6 661; Supplementary Figure 2).

Assessment of Weight Changes

Weight and height were measured at the clinic using standardized protocols. The primary exposure was change in body weight from baseline to year 3 (± 90 days). We classified each woman's change in body weight into 1 of 3 categories, as previously described: (1) weight loss (decrease of ≥5% from baseline); (2) weight gain (increase of ≥5% from baseline); and (3) stable weight (<5% change from baseline) (22). Ten-year changes from baseline used similar categories.

Intentionality of weight loss was assessed among OS participants only at the year 3 visit with the following 2 questions: (1) "In the past two years, did you lose five or more pounds [about ≥2.2 kg] not on purpose at any time" and (2) "In the past two years, did you lose five or more pounds on purpose at any time?" We classified these variables as unintentional and intentional weight loss, respectively. We restricted these analyses to women with objectively confirmed weight loss between baseline and year 3 who reported either intentional or unintentional weight loss, but not both, to aid in the interpretation of findings (N = 3 123; Supplementary Figure 1). Participants also reported behavioral changes for intentional weight loss (eg, diet, and exercise) and potential reasons for unintentional weight loss (eg, stress and depression).

Outcomes

For the main outcome, women were classified as having survived to age 90 or died before this age. We also examined survival to ages 95 and 100 versus death before these ages. Deaths were verified by trained physician adjudicators using hospital records, autopsy or coroner's reports, or death certificates. Periodic linkage to the National Death Index was performed for all participants, including those who were lost to follow-up, for verification if death certificates or medical records were not available. Survival status was ascertained for 96.3% of participants.

Statistical Analysis

Normally and nonnormally distributed covariates were compared across 3-year weight change categories using ANOVA and Kruskal–Wallis tests, respectively. Categorical variables were compared across weight change categories using Chi-square tests.

The association between 3-year weight change and survival to age 90, 95, or 100 years was examined using multivariable logistic regression models. This approach to examining longevity is different from evaluating time to mortality. When examining mortality, or the rate of death irrespective of survival to any given age, the extent to which an exposure predicts survival to old age cannot be determined. In a mortality analysis, more weight is given to earlier-age deaths than later ones because those who do not die are censored. Our approach allows us to examine predictors of survival to the milestone ages of 90, 95, and 100, similar to our previous studies (23,24).

Models were adjusted for confounders selected from the literature on weight change and mortality, including baseline age, study component (OS or CT), race, ethnicity, education, marital status, alcohol consumption, smoking, diet quality measured using the Healthy Eating Index-2015, total physical activity (summarized into metabolic equivalent hours/week), physical function measured using the Rand 36-item Health Survey, body mass index (BMI), and comorbidities including coronary heart disease, diabetes, stroke, cancer, emphysema, and hypertension (2,3,9–11,14,15,25,26). We also examined the association of 10-year weight change with survival in separate models adjusted for these factors. Associations of intentional and unintentional weight loss with survival were examined using a similar approach.

Interactions between baseline BMI and weight changes were analyzed by examining the statistical significance of the cross-product term of weight change and BMI. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2); however, we only examined the latter 3 categories in interaction analyses, as few women were underweight. We also examined interactions with age (<70 vs ≥70 years), as weight loss is more common in older relative to younger adults (27), and smoking status (ever vs never), given that smoking is a major confounder in the association of weight with longevity (15). Interaction analyses were focused on survival to age 90, as this outcome was our main focus.

We performed several sensitivity analyses. To determine whether findings were due to reverse causation, we (1) excluded women with a history of any comorbidity listed above (n = 10 878) and (2) removed women who died within the first 4 years of follow-up after the year 3 visit (n = 1 324). These latter analyses were limited to 3-year weight change analyses, given that 10-year weight change analyses would be more vulnerable to selection bias if we removed women who died after the year 10 visit. We sought to stratify findings by hospitalizations between baseline and year 3 (collected annually among OS participants and semiannually among CT participants), given that fluctuations in weight may be explained by other comorbidities that we did not examine; however, the number of hospitalizations was too low for stratification. We adjusted for (1) the trial arms of the WHI Dietary Modification Trial, which had previously demonstrated weight loss among those in the low-fat dietary intervention arm and (2) the trial arms of the Calcium Plus Vitamin D Supplementation Trial, which had shown small but significant weight reduction in the intervention arm (28,29). Finally, given that weight loss is associated with higher risk of dementia, we adjusted findings for incident cognitive impairment to determine whether this condition is a potential explanation for associations of weight changes with longevity (30). After 2005, cognitive impairment was ascertained by annual surveillance of self-reported moderate or severe memory problems or physician-diagnosed dementia or Alzheimer's disease prior to age 90.

p Values were 2-sided and considered statistically significant at $p < .05$. Statistical analyses were performed using SAS OnDemand for Academics (SAS Institute, Cary, NC).

Results

Participants had a mean baseline age of 69.8 years (SD = 3.9; range = 61.0–81.0 years). Overall 89.5% were White; 5.7% Black; 2.7% Asian; 1.0% more than one race; 0.2% American Indian/Alaskan Native; 0.1% Native Hawaiian/Other Pacific Islander; 0.9% unknown/not reported; and 2.5% Hispanic/Latino. Among the 54 437 women born on or before February 19, 1932, 30 647 (56.3%) survived to age 90. Among the 28 014 women born on or before February 19, 1927, 8 140 (29.1%) survived to age 95. Among the 9 050 women born on or before February 19, 1922, 829 (9.2%) survived to age 100.

In the analytic population (N = 54 437), between baseline and year 3, 68.1% had stable weight; 17.0% had weight loss of ≥5%; and 14.9% had weight gain of ≥5%. Among those with confirmed weight loss, 3 123 women reported on whether they were trying to lose weight during the interval; among these, 1 449 (46.4%) reported intentional weight loss, and 1 674 (53.6%) reported unintentional weight loss. Among women with measured weight between baseline and year 10 (N = 6 661; mean age at year 10, 76.8 [SD 3.5] years), 46.8% had stable weight, 34.9% had weight loss of ≥5%, and 18.3% had weight gain of ≥5%.

Relative to women who experienced 3-year weight loss or weight gain, women with stable weight were less likely to be Black, be current smokers, and have major comorbidities (Table 1). Women who reported intentional weight loss were less physically active, had lower physical function, and were more likely to have hypertension and diabetes relative to other weight categories (Supplementary Table 1). Women who reported unintentional weight loss were more likely to be older, Black, less educated, obese, less physically active, and have major comorbidities relative to other weight categories (Supplementary Table 2).

Three- and 10-year weight change categories significantly differed in the proportion of participants who survived to ages 90, 95, and 100, with the highest proportion among those with stable weight (Tables 2–4). For example, the proportions of survivors to age 90 for 3-year weight change categories were as follows ($p < .001$): stable, 58.7%; gain, 55.0%; and loss, 47.9%. Survival to age 90 was higher among women with intentional (51.4%) relative to unintentional (41.3%) weight loss (Table 2).

Weight Loss

Three-year weight loss of ≥5% vs stable weight was associated with 33% lower odds (OR, 0.67; 95% CI, 0.64–0.71) of survival to age 90, 35% lower odds (OR, 0.65; 95% CI,

Table 1. Baseline Characteristics by Weight Change Category Between Baseline and Year 3

Characteristic	Stable Weight*	Weight Loss*	Weight Gain*	*p* Value
Age at baseline, mean (*SD*), y	69.8 (3.9)	70.2 (4.0)	69.3 (3.7)	<.001
Race, no. (%)				
White	33 307 (89.8)	8 239 (89.2)	7 193 (88.5)	
Black	2 001 (5.4)	582 (6.3)	502 (6.2)	
American Indian/Alaskan Native	75 (0.2)	25 (0.3)	12 (0.2)	
Native Hawaiian/Other Pacific Islander	14 (0.04)	5 (0.05)	10 (0.1)	<.001
Asian	1 011 (2.7)	190 (2.1)	243 (3.0)	
More than one race	357 (1.0)	101 (1.1)	82 (1.0)	
Unknown/not reported	312 (0.8)	92 (1.0)	84 (1.0)	
Ethnicity, no. (%)				
Not Hispanic/Latino	35 971 (97.0)	8 942 (96.8)	7 848 (96.6)	
Hispanic/Latino	903 (2.4)	224 (2.4)	225 (2.8)	.08
Unknown/not reported	203 (0.6)	68 (0.7)	53 (0.7)	
Education, no. (%)				
Less than high school	1 858 (5.0)	585 (6.4)	475 (5.9)	
High school	6 980 (18.9)	1 700 (18.5)	1 547 (19.1)	
Some college	14 039 (38.1)	3 520 (38.4)	3 178 (39.3)	<.001
College graduate	13 977 (37.9)	3 370 (36.7)	2 881 (35.7)	
Income, no. (%)				
<$20 000	6 869 (20.0)	2 026 (23.5)	1 715 (22.8)	
$20 000 to <$50 000	17 800 (51.7)	4 476 (52.0)	3 915 (52.0)	<.001
≥$50 000	9 743 (28.3)	2 114 (24.5)	1 899 (25.2)	
Marital status, no. (%)				
Married/living as married	21 620 (58.5)	5 163 (56.2)	4 330 (53.5)	
Widowed	9 735 (26.4)	2 526 (27.5)	2 324 (28.7)	
Divorced/separated	4 092 (11.1)	1 086 (11.8)	1 108 (13.7)	<.001
Never married	1 482 (4.0)	410 (4.5)	330 (4.1)	
Hormone therapy use, no. (%)				
Never used	13 411 (37.2)	3 530 (39.6)	2 907 (36.8)	
Past user	9 631 (26.7)	2 434 (27.3)	2 149 (27.2)	<.001
Current user	12 982 (36.0)	2 951 (33.1)	2 855 (36.1)	
Smoking status, no. (%)				
Never smoked	20 005 (54.7)	4 923 (54.1)	4 178 (52.3)	
Past smoker	15 111 (41.3)	3 682 (40.5)	3 283 (41.1)	<.001
Current smoker	1 481 (4.1)	495 (5.4)	535 (6.7)	
Alcohol consumption, no. (%)				
Nondrinker	4 299 (11.7)	1 202 (13.2)	971 (12.0)	
Past drinker	6 493 (17.6)	1 814 (19.8)	1 642 (20.3)	<.001
Current drinker	26 021 (70.7)	6 128 (67.0)	5 458 (67.6)	
Body mass index, kg/m^2, no. (%)				
Underweight	351 (1.0)	64 (0.7)	137 (1.7)	
Normal weight	13 903 (37.6)	2 432 (26.9)	3 169 (39.1)	
Overweight	13 371 (36.1)	3 329 (36.9)	2 932 (36.2)	<.001
Obese	9 383 (25.4)	3 210 (35.5)	1 864 (23.0)	
Total physical activity, MET-h/wk, mean (*SD*)	13.3 (13.7)	11.1 (12.3)	13.2 (14.1)	<.001
HEI-2015 diet quality score, mean (*SD*)	67.0 (10.1)	65.3 (10.1)	66.9 (10.2)	<.001
Physical function score, mean (*SD*)	79.8 (19.1)	75.1 (21.6)	78.6 (20.0)	<.001
Comorbidities, no. (%)				
Coronary heart disease	1 014 (2.7)	341 (3.7)	289 (3.6)	<.001
Stroke	534 (1.4)	180 (2.0)	144 (1.8)	<.001
Hypertension	18 481 (51.7)	5 054 (57.1)	4 098 (52.3)	<.001
Diabetes	1 456 (3.9)	523 (5.7)	380 (4.7)	<.001
Cancer	3 618 (9.9)	959 (10.6)	783 (9.8)	.13

Table 1. Continued

Characteristic	Stable Weight*	Weight Loss*	Weight Gain*	*p* Value
Emphysema	1 271 (3.6)	436 (5.1)	318 (4.1)	<.001
Hospitalized from baseline to year 3†	216 (1.9)	72 (2.6)	42 (1.8)	.05
Incident cognitive impairment‡	5 140 (18.2)	1 343 (21.0)	1 095 (18.0)	<.001

Notes: Total *N* = 54 437 (37 077 with stable weight; 9 234 with weight loss; 8 126 with weight gain). Sample sizes for each column may not add up to total due to missing data. SD = standard deviation.
*Weight loss (a decrease of 5% or more from baseline); weight gain (an increase of 5% or more from baseline); and stable weight (change of less than 5% from baseline).
†Medical history update assessing hospitalization was sent annually to OS participants and semiannually to clinical trials participants (total respondents: 11 290 for stable weight; 2 782 for weight loss; and 2 360 for weight gain).
‡Question was collected after 2005 (total respondents: 28 193 for stable weight; 6 389 for weight loss; and 6 085 for weight gain).

Table 2. Multivariable Associations of Weight Change With Survival to Age 90 vs Death Before Age 90 Among Older Women, 1993 to 2022

Variable	No./Total (%) Survived to Age 90, y*	OR (95% CI)†
No./total (%) survived to age 90	30 647/54 437 (56.3)	
3-Y weight change		
Stable weight (within ± 5% change)	21 754/37 077 (58.7)	1.00
Weight loss (≥5%)	4 422/9 234 (47.9)	0.67 (0.64, 0.71)
Intentional‡	745/1 449 (51.4)	0.83 (0.74, 0.94)
Unintentional‡	692/1 674 (41.3)	0.49 (0.44, 0.55)
Weight gain (≥5%)	4 471/8 126 (55.0)	0.95 (0.90, 1.00)
10-Y weight change		
Stable weight (within ± 5% change)	2 003/3 120 (64.2)	1.00
Weight loss (≥5%)	1 187/2 325 (51.1)	0.60 (0.52, 0.69)
Weight gain (≥5%)	747/1 216 (61.4)	1.09 (0.91, 1.31)

*Three-year and 10-year weight change categories significantly differed by survival to age 90 ($p < .001$).
†Models adjusted for age, study component (Observational Study [OS] or Clinical Trial), race, ethnicity, education, marital status, alcohol, smoking, diet quality, physical activity, physical function, body mass index, coronary heart disease, diabetes, stroke, cancer, emphysema, and hypertension.
‡Intention of weight loss was reported at year 3 among women from the OS component only.

0.60–0.71) of survival to age 95, and 38% lower odds (OR, 0.62; 95% CI, 0.49–0.78) of survival to age 100 (Tables 2–4). Ten-year weight loss of ≥5% vs stable weight was associated with 40% lower odds (OR, 0.60; 95% CI, 0.52–0.69) of survival to age 90 and 49% lower odds (OR, 0.51; 95% CI, 0.41–0.63) of survival to age 95 (Tables 2 and 3). These odds ratios, if inverted, also revealed that stable weight increased the odds of longevity by 1.2 to 2-fold for survival to ages 90 to 100 if we use weight loss (either intentional or unintentional) as a comparison group. We did not examine 10-year weight change in relation to survival to age 100 due to inadequate sample size.

Associations with survival were stronger when weight loss was reported to be unintentional vs intentional (Tables 2 and 3). For example, intentional weight loss from baseline to year 3 was associated with 17% lower odds (OR, 0.83; 95% CI, 0.74–0.94) of survival to age 90, whereas unintentional weight loss was associated with 51% lower odds (OR, 0.49; 95% CI, 0.44–0.55) of survival to this age. The main self-reported behaviors for intentional weight loss were change in diet (85.7%), increase in exercise (56.4%), and participation in a commercial weight loss program (16.7%) (Supplementary Table 9). The main self-reported reasons for unintentional weight loss were illness (34.4%), loss of appetite (28.8%), and stress (22.9%) (Supplementary Table 10).

Among 9 234 women who experienced weight loss between baseline and year 3, 1 236 had information on weight at year 10. Among these, 315 (25.5%) had weight loss of ≥5% at year 10, whereas 545 (44.1%) had stable weight and 376 (30.4%) had weight gain of ≥5% at year 10.

Weight Gain

Three-year weight gain of ≥5% vs stable weight was not significantly associated with survival to age 90, 95, or 100 (Tables 2–4). Ten-year weight gain of ≥5% was not significantly associated with survival to age 90 or 95 (Tables 2 and 3); it was not examined in relation to survival to age 100 due to inadequate sample size.

Interactions With BMI, Age, and Smoking

In BMI-stratified analyses, 3-year weight loss of ≥5% was associated with 41% (OR, 0.59; 95% CI, 0.53–0.65), 35% (OR, 0.65; 95% CI, 0.60–0.71), and 22% (OR, 0.78; 95% CI, 0.71–0.85) lower odds of survival to age 90 among normal weight, overweight, and obese women, respectively (Supplementary Table 3; interaction $p < .001$). In the smaller subgroup with data on intentionality, intentional weight loss was associated with reduced odds of survival to age 90 in normal weight, overweight, and obese women, but the confidence interval excluded one only for overweight women due

Table 3. Multivariable Associations of Weight Change With Survival to Age 95 vs Death Before Age 95 Among Older Women, 1993 to 2022

Variable	No./Total (%) Survived to Age 95, y*	OR (95% CI)†
No./total (%) survived to age 95	8 140/28 014 (29.1)	
3-Y weight change		
Stable weight (within ± 5% change)	5 974/19 098 (31.3)	1.00
Weight loss (≥5%)	1 123/5 191 (21.6)	0.65 (0.60, 0.71)
Intentional‡	166/687 (24.2)	0.77 (0.63, 0.94)
Unintentional‡	175/1 096 (16.0)	0.44 (0.37, 0.53)
Weight gain (≥5%)	1 043/3 725 (28.0)	0.94 (0.86, 1.02)
10-Y weight change		
Stable weight (within ± 5% change)	562/1 476 (38.1)	1.00
Weight loss (≥5%)	342/1 347 (25.4)	0.51 (0.41, 0.63)
Weight gain (≥5%)	174/501 (34.7)	0.85 (0.64, 1.12)

*Three-year and 10-year weight change categories significantly differed by survival to age 95 ($p < .001$).
†Models adjusted for age, study component (Observational Study [OS] or Clinical Trial), race, ethnicity, education, marital status, alcohol, smoking, diet quality, physical activity, physical function, body mass index, coronary heart disease, diabetes, stroke, cancer, emphysema, and hypertension.
‡Intention of weight loss was reported at year 3 among women from the OS component only.

Table 4. Multivariable Association of 3-Year Weight Change With Survival to Age 100 vs Death Before Age 100 Among Older Women, 1993 to 2022

Variable	No./Total (%) Survived to Age 100, y*	OR (95% CI)†
No./total (%) survived to age 100	829/9 050 (9.2)	
3-Y weight change‡		
Stable weight (within ± 5% change)	621/6 137 (10.1)	1.00
Weight loss (≥5%)	113/1 858 (6.1)	0.62 (0.49, 0.78)
Weight gain (≥5%)	95/1 055 (9.0)	0.94 (0.73, 1.22)

*Three-year weight change categories significantly differed by survival to age 100 ($p < .001$).
†Models adjusted for age, study component (Observational Study or Clinical Trial), race, ethnicity, education, marital status, alcohol, smoking, diet quality, physical activity, physical function, body mass index, coronary heart disease, diabetes, stroke, cancer, emphysema, and hypertension.
‡Intention of weight loss could not be examined due to low sample size.

to smaller sample sizes within strata. Unintentional weight loss was more strongly related to lower odds of survival to age 90 than intentional weight loss across all BMI categories: OR for normal weight, 0.48; 95% CI, 0.40–0.57; OR for overweight, 0.49; 95% CI, 0.40–0.60; and OR for obese, 0.56; 95% CI, 0.43–0.72. Three-year weight gain of ≥5% was not significantly associated with survival to age 90 across all BMI categories. There was no significant interaction between 10-year weight change and BMI. Findings did not significantly vary by baseline age (Supplementary Table 4) or smoking (Supplementary Table 5).

Sensitivity Analyses

Findings were similar when excluding women with a history of comorbidities at baseline (Supplementary Table 6) or those who died within the first 4 years of follow-up (Supplementary Table 7), and after additionally adjusting for participation in the Dietary Modification and Calcium plus Vitamin D Supplementation trials (Supplementary Table 8). Incident cognitive impairment was higher in women who experienced weight loss of ≥5%, particularly unintentional weight loss, relative to women with stable weight or weight gain of ≥5% (Table 1; Supplementary Tables 1 and 2). After adjusting for incident cognitive impairment, associations of weight loss, including both intentional and unintentional, with longevity were slightly attenuated, whereas associations for weight gain were similar (Supplementary Table 11).

Discussion

Three-year weight loss of ≥5% vs stable weight was associated with lower odds of survival to ages 90, 95, and 100 among older women. Though both intentional and unintentional weight loss were associated with reduced odds of longevity, unintentional weight loss was more strongly associated with lower odds of longevity relative to intentional weight loss, and this finding was observed among normal weight, overweight, and obese women. Weight gain of ≥5% was not significantly associated with survival to ages 90, 95, or 100. Findings also showed that stable weight increased the odds of longevity by 1.2 to 2-fold relative to weight loss of ≥5%. Associations were similar for 10-year weight changes.

Weight loss has been associated with higher mortality risk in older adults (1,2,9,10,31). In a study among older Japanese adults, 3-year, 6–7-year, and 12–13 year weight loss of ≥5% vs stable weight was associated with 36%, 36%, and 31% higher mortality risk, respectively, independent of sociodemographic characteristics, lifestyle behaviors, and comorbidities (9). Weight loss was generally associated with higher mortality risk across BMI categories, similar to our study (9). In the

Cardiovascular Health Study, 3-year weight loss of ≥5% vs stable weight was associated with 67% higher mortality risk, and every one-unit decrease in BMI measured at 67–75 years was associated with 53% lower odds of survival to age 90 (10,32). A recent study of 16 523 community-dwelling older adults found that, relative to stable weight, weight loss of 5% to 10% and more than 10% was associated with 33% and 289% higher mortality risk in men, respectively, and 26% and 114% higher mortality risk in women, respectively (33).

The relationship between weight loss and mortality varies according to the intentionality of weight loss (16–18,34–39). Among British men 56–75 years, unintentional weight loss vs stable weight was associated with 71% higher mortality risk, whereas intentional weight loss was associated with 41% lower mortality risk (34). Among 161 738 middle-aged adults, increased frequency of intentionally losing ≥5 pounds in midlife was associated with lower mortality risk (35). We found that both intentional and unintentional weight loss were associated with lower odds of longevity, though the magnitude of the association was greater for unintentional weight loss. This finding is consistent with a prior study among male veterans ≥65 years, which observed that mortality was increased among weight losers, irrespective of the intentionality (39).

Intentional weight loss for personal reasons has been associated with lower mortality, whereas intentional weight loss due to ill health has been associated with higher mortality (34). The primary self-reported behaviors for intentional weight loss in our study included changes in diet and exercise and participation in commercial weight loss programs. Although we found that women who reported intentional weight loss had lower odds of longevity, it is possible that some proportion of self-reported intentional weight loss in actuality was unintentional weight loss. Unintentional weight loss occurs in 15% to 20% of older adults, and its most common etiologies include malignancy, nonmalignant gastrointestinal disease, and psychiatric conditions (40). It is important to note that perceived intentionality of weight loss may be influenced by the many societal pressures to lose weight, especially among women, and therefore overestimate the behavioral changes underlying experienced weight loss in older adults.

Several randomized controlled trials (RCT) suggest that intentional weight loss lowers mortality risk in adults (37,41). Other trials have shown that caloric restriction is favorably associated with biomarkers of aging, including slowing the pace of aging, decreasing fasting insulin, improving exercise capacity, and decreasing levels of cardiometabolic risk factors (eg, total cholesterol) (42–45). A meta-analysis of 15 RCTs of intentional weight loss in obese adults (N = 17 186; 53% female; mean age = 52) observed that risk of all-cause mortality was 15% lower for those randomized to weight loss compared to nonweight loss groups (37); findings were similar when restricted to trials with mean age ≥55 years. Another meta-analysis of 34 RCTs in 21 699 participants (with mean ages ranging from 43.6 to 70.3 years) found that weight loss interventions were associated with 18% reduction in all-cause mortality risk (41). The Look AHEAD trial among 5 145 overweight/obese adults ages 45–76 years with type 2 diabetes found that, although all-cause mortality did not differ significantly between the intensive lifestyle intervention (ILI) and diabetes support and education (DSE) groups during 16.7 years of follow-up, participants in the ILI who lost ≥10% body weight in the first year of the intervention had 21% reduced risk of mortality relative to DSE (46). Paradoxically, in a recent postintervention analysis (year 8 to a median of 16 years) of 3 999 Look AHEAD participants (60% women; mean baseline age = 58.7 years), irrespective of randomization to the ILI, mortality was *higher* in participants with steady weight loss (18%) and *highest* in those with steep weight loss (30%) relative to those who gained weight (10%) or had stable weight (14%) during the postintervention period (47). Those in the steep weight loss group were older, were more likely to be obese, had longer duration of diabetes, and had higher prevalence of multimorbidity at baseline compared to participants who were stable weight. At year 8 (end of the intervention), steep weight losers had higher levels of multimorbidity, frailty, and depression relative to stable weight individuals. Further, at year 8, steep weight losers reported fewer intentional weight loss strategies, suggesting that they were experiencing unintentional weight loss that may have been due to poor health. However, prior trials of intentional weight loss such as Look AHEAD did not examine survival to ages 90 to 100 and were not largely focused on weight changes in older adults, which was our specific focus. Among obese women in the subset with intentionality data, we observed the same pattern of results as that for the overall cohort: intentional weight loss was associated with 12% reduced odds of survival to age 90 (OR, 0.88; 95% CI, 0.73–1.06), whereas unintentional weight loss was associated with 44% reduced odds of survival to age 90 (OR, 0.56; 95% CI, 0.43–0.72). In agreement with the conclusion of the recent Look AHEAD analysis , unintentional weight loss could serve as an important indicator of underlying poor health and predictor of decreased longevity in the clinical setting.

Evidence on the association of weight gain with mortality among older adults is mixed (1–3,10). Short- and long-term weight gain of ≥5% were not associated with mortality in older Japanese adults, similar to a study in the Cardiovascular Health Study (9,10). Importantly, weight gain from early to middle adulthood may be related to poor health outcomes later in life (3,15,48). For example, 2 large, long-term cohorts observed that 5-kg weight gain from 18 to 55 years was associated with higher risk of type 2 diabetes, cardiovascular disease, and mortality (15). Thus, early and midlife weight gain appear to increase risk of poor health outcomes later in life, whereas the association in older adults is less clear.

A potential limitation of our study is that women were >60 years at baseline and thus may have been more likely to achieve longevity. Therefore, findings may not be generalizable to the general population of adult women across a broader age range. Although we controlled for preexisting diseases, we cannot completely rule out residual confounding due to ill health resulting in weight loss. However, findings were similar when excluding women with major comorbidities at baseline or those who died within the first 4 years of follow-up. The sample was mostly White, which limited our ability to evaluate racial and ethnic differences. Self-reported intentionality of weight loss was available only in a subset. Given the observational nature of our study, residual confounding due to unmeasured factors may explain the associations of weight loss with longevity observed in our study. Strengths include a large sample with long-term follow-up, objectively measured weight changes at multiple time points, information on numerous potential confounders, and large numbers of women who survived to exceptional ages.

In conclusion, weight loss of ≥5% but not weight gain was associated with lower odds of longevity, more strongly so among women with unintentional weight loss. These findings, in the context of the totality of the evidence, suggest that blanket recommendations for weight loss in older women are unlikely to lead to better survival to advanced ages. We recognize that these data do not affect clinical recommendations for moderate weight loss when needed to achieve positive health outcomes, particularly for obese and severely obese persons, but these data support close monitoring of the amount and speed of weight loss, particularly when unintentional, as an indicator of underlying poor health and predictor of decreased lifespan in older women. Importantly, this study supports the promotion of weight stability as a useful predictor of longevity in older women.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None: A.H.S., J.E.M., M.A., D.L., S.W.S., L.V.H., R.A.W., H.B., F.K.T., B.H., Y.S., E.S.L., J.W.W., M.S.L., M.J.N., J.L., P.F.S., G.M., A.Z.L. R.J.O. declares research grants from Purjes Foundation and Greenbaum Foundation, and is an advisory board member of Mesuron, Inc. with stock option interest.

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The National Heart, Lung, and Blood Institute has representation on the Women's Health Initiative Steering Committee, which governed the design and conduct of the study, the interpretation of the data, and preparation and approval of manuscripts.

The short list of Women's Health Initiative investigators includes the following:

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

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References

1. Alharbi TA, Paudel S, Gasevic D, Ryan J, Freak-Poli R, Owen AJ. The association of weight change and all-cause mortality in older adults: a systematic review and meta-analysis. *Age Ageing*. May 05, 2021;50(3):697–704. doi:10.1093/ageing/afaa231
2. Bamia C, Halkjaer J, Lagiou P, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health Study. *J Intern Med*. August 2010;268(2):133–144. doi:10.1111/j.1365-2796.2010.02219.x
3. Chen C, Ye Y, Zhang Y, Pan XF, Pan A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. *Br Med J*. October 16, 2019;367:l5584. doi:10.1136/bmj.l5584
4. Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A. Association of body mass index and weight change with all-cause mortality in the elderly. *Am J Epidemiol*. May 15, 2006;163(10):938–949. doi:10.1093/aje/kwj114
5. Dahl AK, Fauth EB, Ernsth-Bravell M, Hassing LB, Ram N, Gerstof D. Body mass index, change in body mass index, and survival in old and very old persons. *J Am Geriatr Soc*. April 2013;61(4):512–518. doi:10.1111/jgs.12158
6. de Hollander EL, Van Zutphen M, Bogers RP, Bemelmans WJ, De Groot LC. The impact of body mass index in old age on cause-specific mortality. *J Nutr Health Aging*. January 2012;16(1):100–106. doi:10.1007/s12603-011-0077-6
7. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc*. February 2010;58(2):234–241. doi:10.1111/j.1532-5415.2009.02677.x
8. Gulsvik AK, Thelle DS, Mowé M, Wyller TB. Increased mortality in the slim elderly: a 42 years follow-up study in a general population. *Eur J Epidemiol*. 2009;24(11):683–690. doi:10.1007/s10654-009-9390-3
9. Murayama H, Liang J, Shaw BA, et al. Short-, medium-, and long-term weight changes and all-cause mortality in old age: findings from the National Survey of the Japanese Elderly. *J Gerontol A Biol Sci Med Sci*. October 13, 2021;76(11):2039–2046. doi:10.1093/gerona/glab052
10. Newman AB, Yanez D, Harris T, Duxbury A, Enright P L, Fried L P; Cardiovascular Study Research Group. Weight change in old age and its association with mortality. *J Am Geriatr Soc*. October 2001;49(10):1309–1318. doi:10.1046/j.1532-5415.2001.49258.x
11. Somes GW, Kritchevsky SB, Shorr RI, Pahor M, Applegate WB. Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program. *Am J Epidemiol*. July 15, 2002;156(2):132–138. doi:10.1093/aje/kwf019
12. Wu CY, Chou YC, Huang N, Chou YJ, Hu HY, Li CP. Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. *PLoS One*. 2014;9(7):e102589. doi:10.1371/journal.pone.0102589
13. Xie W, Lundberg DJ, Collins JM, et al. Association of weight loss between early adulthood and midlife with all-cause mortality risk

in the US. *JAMA Netw Open*. 2020;3(8):e2013448. doi:10.1001/jamanetworkopen.2020.13448
14. Yu E, Ley SH, Manson JE, et al. Weight history and all-cause and cause-specific mortality in three prospective cohort studies. *Ann Intern Med*. May 02, 2017;166(9):613–620. doi:10.7326/M16-1390
15. Zheng Y, Manson JE, Yuan C, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. *JAMA*. July 18, 2017;318(3):255–269. doi:10.1001/jama.2017.7092
16. Gregg EW, Gerzoff RB, Thompson TJ, Williamson DF. Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. *Ann Intern Med*. March 04, 2003;138(5):383–389. doi:10.7326/0003-4819-138-5-200303040-00007
17. French SA, Folsom AR, Jeffery RW, Williamson DF. Prospective study of intentionality of weight loss and mortality in older women: the Iowa Women's Health Study. *Am J Epidemiol*. March 15, 1999;149(6):504–514. doi:10.1093/oxfordjournals.aje.a009844
18. Wijnhoven HA, van Zon SK, Twisk J, Visser M. Attribution of causes of weight loss and weight gain to 3-year mortality in older adults: results from the Longitudinal Aging Study Amsterdam. *J Gerontol A Biol Sci Med Sci*. October 2014;69(10):1236–1243. doi:10.1093/gerona/glu005
19. Volpi E, Nazemi R, Fujita S. Muscle tissue changes with aging. *Curr Opin Clin Nutr Metab Care*. July 2004;7(4):405–410. doi:10.1097/01.mco.0000134362.76653.b2
20. Alley DE, Metter EJ, Griswold ME, et al. Changes in weight at the end of life: characterizing weight loss by time to death in a cohort study of older men. *Am J Epidemiol*. September 01, 2010;172(5):558–565. doi:10.1093/aje/kwq168
21. Design of the Women's Health Initiative Clinical Trial and Observational Study. The Women's Health Initiative Study Group. *Control Clin Trials*. February 1998;19(1):61–109. doi:10.1016/s0197-2456(97)00078-0
22. Crandall CJ, Yildiz VO, Wactawski-Wende J, et al. Postmenopausal weight change and incidence of fracture: post hoc findings from Women's Health Initiative Observational Study and Clinical Trials. *Br Med J*. January 27, 2015;350:h25. doi:10.1136/bmj.h25
23. Shadyab AH, Macera CA, Shaffer RA, et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. *Menopause*. January 2017;24(1):35–44. doi:10.1097/GME.0000000000000710
24. Shadyab AH, Manson JE, Luo J, et al. Associations of coffee and tea consumption with survival to age 90 years among older women. *J Am Geriatr Soc*. September 2020;68(9):1970–1978. doi:10.1111/jgs.16467
25. Krebs-Smith SM, Pannucci TE, Subar AF, et al. Update of the Healthy Eating Index: HEI-2015. *J Acad Nutr Diet*. September 2018;118(9):1591–1602. doi:10.1016/j.jand.2018.05.021
26. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health survey 1.0. *Health Econ*. October 1993;2(3):217–227. doi:10.1002/hec.4730020305
27. Williamson DF. Descriptive epidemiology of body weight and weight change in U.S. adults. *Ann Intern Med*. October 01, 1993;119(7 Pt 2):646–649. doi:10.7326/0003-4819-119-7_part_2-199310011-00004
28. Howard BV, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA*. January 04, 2006;295(1):39–49. doi:10.1001/jama.295.1.39
29. LaCroix AZ, Kotchen J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. May 2009;64(5):559–567. doi:10.1093/gerona/glp006
30. Lee CM, Woodward M, Batty GD, et al. Association of anthropometry and weight change with risk of dementia and its major subtypes: a meta-analysis consisting 2.8 million adults with 57 294 cases of dementia. *Obes Rev*. April 2020;21(4):e12989. doi:10.1111/obr.12989
31. Park SY, Wilkens LR, Maskarinec G, Haiman CA, Kolonel LN, Marchand LL. Weight change in older adults and mortality: the Multiethnic Cohort Study. *Int J Obes (Lond)*. February 2018;42(2):205–212. doi:10.1038/ijo.2017.188
32. Odden MC, Rawlings AM, Arnold AM, et al. Patterns of cardiovascular risk factors in old age and survival and health status at 90. *J Gerontol A Biol Sci Med Sci*. October 15, 2020;75(11):2207–2214. doi:10.1093/gerona/glaa043
33. Hussain SM, Newman AB, Beilin LJ, et al. Associations of change in body size with all-cause and cause-specific mortality among healthy older adults. *JAMA Netw Open*. April 03, 2023;6(4):e237482. doi:10.1001/jamanetworkopen.2023.7482
34. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med*. May 09, 2005;165(9):1035–1040. doi:10.1001/archinte.165.9.1035
35. Willis EA, Huang WY, Saint-Maurice PF, et al. Increased frequency of intentional weight loss associated with reduced mortality: a prospective cohort analysis. *BMC Med*. September 17, 2020;18(1):248. doi:10.1186/s12916-020-01716-5
36. De Stefani FDC, Pietraroia PS, Fernandes-Silva MM, Faria-Neto J, Baena CP. Observational evidence for unintentional weight loss in all-cause mortality and major cardiovascular events: a systematic review and meta-analysis. *Sci Rep*. October 18, 2018;8(1):15447. doi:10.1038/s41598-018-33563-z
37. Kritchevsky SB, Beavers KM, Miller ME, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS One*. 2015;10(3):e0121993. doi:10.1371/journal.pone.0121993
38. Locher JL, Roth DL, Ritchie CS, et al. Body mass index, weight loss, and mortality in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. December 2007;62(12):1389–1392. doi:10.1093/gerona/62.12.1389
39. Wallace JI, Schwartz RS, LaCroix AZ, Uhlmann RF, Pearlman RA. Involuntary weight loss in older outpatients: incidence and clinical significance. *J Am Geriatr Soc*. April 1995;43(4):329–337. doi:10.1111/j.1532-5415.1995.tb05803.x
40. Gaddey HL, Holder KK. Unintentional weight loss in older adults. *Am Fam Physician*. July 01, 2021;104(1):34–40.
41. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *Br Med J*. November 14, 2017;359:j4849. doi:10.1136/bmj.j4849
42. Waziry R, Ryan CP, Corcoran DL, et al. Effect of long-term caloric restriction on DNA methylation measures of biological aging in healthy adults from the CALERIE trial. *Nat Aging*. March 2023;3(3):248–257. doi:10.1038/s43587-022-00357-y
43. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. Jan 05, 2016;315(1):36–46. doi:10.1001/jama.2015.17346
44. Ravussin E, Redman LM, Rochon J, et al.; CALERIE Study Group. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. *J Gerontol A Biol Sci Med Sci*. September, 2015;70(9):1097–1104. doi:10.1093/gerona/glv057
45. Heilbronn LK, de Jonge L, Frisard MI, et al.; Pennington CALERIE Team. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA*. April 05, 2006;295(13):1539–1548. doi:10.1001/jama.295.13.1539
46. Group LAR. Effects of intensive lifestyle intervention on all-cause mortality in older adults with type 2 diabetes and overweight/obesity: results from the Look AHEAD Study. *Diabetes Care*. March 21, 2022;45(5):1252–1259. doi:10.2337/dc21-1805

47. Wing RR, Neiberg RH, Bahnson JL, et al.; on behalf on the Look AHEAD Research Group. Weight change during the postintervention follow-up of Look AHEAD. *Diabetes Care*. April 14, 2022;45(6):1306–1314. doi:10.2337/dc21-1990

48. Jia G, Shu XO, Liu Y, et al. Association of adult weight gain with major health outcomes among middle-aged Chinese persons with low body weight in early adulthood. *JAMA Netw Open*. December 02, 2019;2(12):e1917371. doi:10.1001/jamanetworkopen.2019.17371