eAppendix

Technical Details and Additional Sensitivity Analyses to Manuscript "Weight Change, Initial BMI, and Mortality among Middle- and Older-Aged Adults"

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In this document, we offer a more comprehensive description of the data, methods and models used in the manuscript, and we show the results of additional sensitivity analyses that were either not detailed or not discussed in the manuscript.

Data and participants

This is a prospective cohort study. We use the nationally representative Health and Retirement Study (HRS) to study the relationship between two year weight change and mortality by initial body mass index (BMI; kg/m^2) among 50 to 70 year old adults. The HRS is a nationally representative panel survey of Americans aged 50 and over and their spouses.[1] The study is ongoing, and currently covers the years 1992-2006. The HRS is sponsored by the National Institute of Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. In addition to the survey information obtained directly from the HRS, we use data on month and year of death from the National Death Index (NDI). For the HRS participants, the NDI based month and year of death information comes from the HRS Tracker file which is downloadable from the University of Michigan Health and Retirement Study website.[2] We merge the Tracker file to the HRS data using the code provided by the HRS website.

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The HRS has five entry cohorts: the initial HRS cohort, born in 1931-1941 and first interviewed in 1992; the Study of Assets and Health Dynamics Among the Oldest Old (AHEAD) cohort, born in 1923 or earlier and first interviewed in 1993; the Children of Depression (CODA) cohort, born 1924 to 1930 and first interviewed in 1998; the War Baby (WB) cohort, born 1942 to 1947 and first interviewed in 1998; and the Early Baby Boomer (EBB) cohort, born 1948 to 1953 and first interviewed in 2004. Our goal is to study the relationship between weight change and mortality by initial BMI among people aged 50 to 70 years. Thus we include primary respondents and their spouses who were between 50 and 70 years old at the first interview. All primary respondents in the HRS and WB cohorts were between 50 and 70 at the first interview, so these respondents and their spouses who were age 50-70 at the first interview are included. Primary respondents in the CODA cohort are 68-74 years old at the first interview. From this cohort we include those who were 68-70 years old at the first interview. The results are robust to the inclusion or exclusion of subjects from the CODA cohort. The Early Baby Boomers (EBB) cohort is completely excluded from the analysis because for this cohort no follow-up after the second interview is available. The AHEAD cohort is excluded for two reasons: (1) the questionnaire for the AHEAD cohort was not the same as it was for the other cohorts in the first two interviews, and (2) primary respondents in the AHEAD cohort were all aged 70 or over at the first interview.

The total number of subjects in our data is 14,823 (11,774 from HRS; 2,259 from WB; 790 from CODA) before further exclusions. We exclude 464 subjects because of item non-response and 2 subjects because they had died according to the NDI file but were alive according to HRS. There were 93 subjects who had died according to HRS between two consecutive waves but whose month and year of death information was not available from the NDI file. We code these subjects

as deceased, and estimate the death time to be in between the interview where the person was last seen alive and the next interview. We also tried excluding these 93 people form the analysis, and using the date of the last interview when they were alive as the basis for a censored survival time (so that they were treated as 'alive when last seen'). The results were robust to these changes.

We exclude 808 observations because of attrition before the second interview, and we further exclude 445 subjects because their weight change was more than 5 BMI units during the approximately two year observation period from the first to the second interview. We exclude these subjects because our aim is to analyze the effects of small and large weight changes, not extreme weight changes (only 3.3 % had a weight change larger than 5 BMI units).

The remaining sample size is 14,823 – 464 – 2 – 808 – 445 = 13,104 subjects and 1,983 deaths. The number and percentage of subjects by cohort is 10,404 (79.4 %) for the original HRS cohort; 2,010 (15.3 %) for the WB cohort; and 690 (5.3 %) for the CODA cohort. The number and percentage of subjects in 5-year age groups is 5,504 (42.0 %) in the age group 50-54; 4,465 (34.1 %) in the age group 55-59; 2,017 (15.4 %) in the age group 60-64; and 1,118 (8.5 %) in the age group 65-69. eTable 1 shows the characteristics of the analyzed sample of 13,104 subjects, and also the characteristics for those who were lost due to attrition before the second interview and who were excluded because their weight change was larger than 5 BMI units. Compared to the analyzed sample, the 808 persons who were lost due to attrition before the second interview were older (57.5 vs 56.9 years), less likely to be women (43.5 vs 50.3 %), less likely to be white (65.2 vs. 74.1 %), had lower education (11.6 vs. 12.3 years), had worse self-rated health (2.9 vs. 3.4) and had higher prevalence of pre-existing diseases. Those who were excluded because of very large weight change (>5 BMI units) also have different characteristics than the analyzed sample: these 445 excluded subjects are more likely to be women (64.3 vs 50.3 %), less likely to be white

(51.9 vs. 74.1 %), had lower education (10.8 vs. 12.3 years), had worse self-rated health (2.8 vs. 3.4) and had higher prevalence of pre-existing diseases. Thus the analyzed sample is more educated and healthier both in terms of self-rated health and diagnosed diseased than those who were lost due to attrition and those who were excluded because of a very large weight change. To the extent that our results may be driven by undiagnosed disease affecting both weight change and risk of death, the fact that our analyzed sample is healthier than those who were excluded lends a conservative bias to our estimates.

Variables

Survival time is measured starting from the second interview and censored at the last interview, which for most subjects is the year 2006 interview. Because of attrition due to causes other than death, the last interview is from an earlier wave for 1,669 subjects (12.7% =1,669/13,104). We also note that the timing of the first interview depends on the subject, as the original HRS cohort entered the study in 1992 and the WB and CODA cohorts entered the study in 1998.

Weight change is measured between the first two interviews, and survival time is measured starting from the second interview. eFigure 1 shows the ordering of events for four hypothetical subjects and whether they were included in the study and censored. The first hypothetical subject was alive from the first interview to the year 2006 interview. This subject is included in the study, and the survival time is censored at the year 2006 interview date. The second hypothetical subject was lost due to attrition between the second and last (year 2006) interview. This person is included in the study with censored survival time. The third subject died between the second interview and the year 2006 interview. This person is included in the study. The information about exact death time (month, year) may come from the NDI file or, if the NDI file does not

have a record for this subject (as is the case for 93 subjects), the death time is estimated to be in between the interview where the person was last seen alive and the next interview. The fourth subject is excluded from the study because of attrition due to death or other reasons before the second interview. These subjects are excluded because the key independent variable, weight change, is not observed.

Initial weight status is measured as BMI (BMI = kg/m^2) and constructed from self-reported weight and height at the first interview. Weight change is measured in BMI units. We categorize weight change as large weight loss (3.0-5.0 BMI units), small weight loss (1.0-2.9 units), large weight gain (3.0-5.0 units) and small weight gain (1.0-2.9 units). The reference group, stable weight, is BMI change smaller than 1 BMI units. For a 5 foot 5 inches (1.65m) tall person stable weight is +/- 6.0 pounds of change (+/- 2.8kg), small weight change is 6.0-18.0 pounds (2.8-8.2kg), and large weight change is 18.0-30.0 pounds (8.2-13.6kg). For a 6 foot (1.82m) tall person stable weight is +/- 7.3 pounds of change (+/- 3.3kg), small weight change is 7.3-21.9 pounds (3.3-9.8kg), and large weight change is 21.9-36.5 pounds (9.9-16.6kg). Our results were not sensitive to small changes in the cutoff points for BMI change.

We adjust for both self-reported health conditions and self-rated health. HRS has data on eight conditions based on responses to two types of questions: “Has a doctor ever told you that you have ...” (first interview) and, if in the first interview the respondent answered not having the condition in question, “Since we last talked to you, that is since [last interview date], has a doctor told you that you have ...” (second interview). If the respondent answered affirmatively at the initial interview, they were asked about the same condition also at the second interview, where they had the chance to dispute having had the condition in question. If the respondent had

answered affirmative at the first interview but disputed ever having had the condition in the second interview, they were coded as not having the condition.

For each of the eight health conditions, we construct two indicator variables. The first indicates having the condition at the first interview. The second indicator is for conditions diagnosed between the first and second interview.

We adjust for initial self-rated health and changes in self-rated health between the first and second interviews. Self-rated health is reported as excellent, very good, good, fair or poor in both the first and second interview. We code these to a 5 point continuous variable with 5 = excellent and 1 = poor. Change in self-rated health (continuous) ranges from -4 (from excellent to poor) to +4 (from poor to excellent). Using categorical rather than continuous variables did not change our results.

Additional control variables are sex, age (years), cohort (HRS/CODA/WB), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (years), physical activity (indicator for 3 or more times vigorous physical activity per week), smoking (never/former/current) and household income ($1,000). We use household income on original (linear) scale; using logged household income instead of linear did not change the results.

Statistical models

We use proportional hazard models to estimate the hazard ratios for weight change. We estimate four different models: Model 1a estimates the main effect of weight change on mortality and adjusts for initial BMI, basic demographic characteristics, and behavioral variables but not for health status. Model 1b is like Model 1a, but adjusts, in addition, for health status at the first

interview and changes in health status between the first and second interview. Model 2a extends Model 1a by including an interaction between weight change and initial BMI; this allows us to estimate the modifying effect of initial BMI on the association between weight change and mortality. Model 2b similarly extends Model 1b by including this interaction.

The model equations for Models 1a-2b are

(1a) $h(t;\mathbf{x}) = h(t)\exp\left(\boldsymbol{\beta}_1'\mathbf{WeightChange} + \boldsymbol{\beta}_2'\mathbf{InitBMI} + \boldsymbol{\beta}_3'\mathbf{D}\right)$;

(1b) $h(t;\mathbf{x}) = h(t)\exp\left(\boldsymbol{\beta}_1'\mathbf{WeightChange} + \boldsymbol{\beta}_2'\mathbf{InitBMI} + \boldsymbol{\beta}_3'\mathbf{D} + \boldsymbol{\beta}_4'\mathbf{H}\right)$;

(2a) $h(t;\mathbf{x}) = h(t)\exp\left(\boldsymbol{\beta}_1'\mathbf{WeightChange} + \boldsymbol{\beta}_2'\mathbf{InitBMI} + \boldsymbol{\beta}_{12}'\mathbf{ChangeInit} + \boldsymbol{\beta}_3'\mathbf{D}\right)$; and

(2b) $h(t;\mathbf{x}) = h(t)\exp\left(\boldsymbol{\beta}_1'\mathbf{WeightChange} + \boldsymbol{\beta}_2'\mathbf{InitBMI} + \boldsymbol{\beta}_{12}'\mathbf{ChangeInit} + \boldsymbol{\beta}_3'\mathbf{D} + \boldsymbol{\beta}_4'\mathbf{H}\right)$,

where $\mathbf{BMIChange}$ is a vector for BMI change variables (indicators for large weight loss, small weight loss, large weight gain, and small weight gain; stable weight is the reference group); $\mathbf{InitBMI}$ is continuous initial BMI and squared initial BMI; $\mathbf{ChangeInit}$ is the interaction between weight change and initial BMI; $\mathbf{D}$ is for demographic and behavioral variables (age, age squared, sex, race/ethnicity, education, household income, HRS cohort, smoking, physical activity); and $\mathbf{H}$ is for health variables (pre-existing conditions and conditions diagnosed during the weight change period, self-rated health at the first interview and changes in self-rated health during the weight change period).

We include squared BMI as a control variable in all models in order to capture the non-linear effect of initial BMI.[3-8] In modeling an interaction between weight change and initial BMI, we

use the categorical weight change variables and the continuous variable for initial BMI. We do so because preliminary analyses with initial BMI modeled as a categorical variable suggested that the effect of weight change depends linearly on initial BMI, and modeling the interaction effect with continuous BMI is statistically more efficient than coding the initial BMI as a categorical variable. We do not include the interaction between weight change and the quadratic initial BMI term because: (i) preliminary analyses indicated that the modifying effect of initial BMI on the weight change-mortality relationship is linear; (ii) the interaction effect, if used, would be statistically insignificant ($P > 0.10$); and (iii) sensitivity analyses suggested that the results are robust to the inclusion or exclusion of the quadratic BMI-weight change interaction.

The net effect of weight change on mortality hazard ratio by initial BMI is estimated as follows. For Models 1a-1b, where there is no interaction between initial BMI and weight change, the net effect is:

(3) Net effect at a given initial BMI level = $\boldsymbol{\beta}_1$,

where $\boldsymbol{\beta}_1$ is a vector representing the coefficients for weight change (large weight loss, small weight loss, large weight gain, small weight gain). The effects are constant across initial BMI because the models omit the weight change-initial BMI interaction. Models 2a and 2b add an interaction between weight change and initial BMI, allowing the effects of weight change depend on initial BMI. In these models, the net effect of weight change on mortality hazard ratio by initial BMI is estimated as

(4) Net effect at a given initial BMI level = $\boldsymbol{\beta}_1' + \boldsymbol{\beta}_{12}' BMI$,

where $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_{12}$ are vectors representing the main effect of weight change and the weight change-intitial BMI interaction, respectively. Since the coefficients are vectors, the net effect is also a vector, consisting of the net effects for large weight loss, small weight loss, large weight gain, and small weight gain at a given initial BMI level. Using equation (4) we estimate the net effects of weight change from initial BMI levels ranging from 18.0 to 40.0.

We estimate the model parameters by using the SAS PROC TPHREG.[9] More specifically, we estimate the parameters by maximizing the partial likelihood using the Newton-Raphson algorithm, and handle ties with the approximate likelihood method.[10] We use time-on-study for time scale and adjust for age and age squared; this approach performed well in a study comparing six different choices of time scale in cohort studies.[11] We tested the proportional hazards assumption in two ways. First, we visually inspected the Kaplan-Meier survival curves and log of the negative log of the survival curves by weight change category. No deviations from the proportional hazards assumption were detected. Second, we interacted weight change with log of time on study in Models 1a and 1b, and in Models 2a and 2b we interacted weight change and weight change-initial BMI interaction with time on study. Statistical tests for the interactions with time were did not reveal any strong time dependencies. Thus the proportional hazards assumption seems reasonable. We use the robust sandwich variance-covariance estimator[12] to take into account the clustering of subjects within households.

Sensitivity analyses

We estimate various alternative models to assess the robustness of our findings. The results of these analyses are shown in eTable 2. These results are to be compared to our main model, Model 2b from the manuscript, whose results are also shown in eTable 2.

First, we conduct sensitivity checks to strengthen our confidence that the observed association between weight change and mortality is not driven in any substantive way by observed or unobserved illness. We do this by estimating the effects of weight change on mortality by initial BMI using alternative model specifications which help us understand the influence of underlying illness on our main results. We estimate the weight change-mortality association for (i) those who did not have *any* diagnosed conditions at the first interview (Model A1), (ii) for those whose self-rated health was good, very good or excellent at the first interview (Model A2), (iii) for those who did not die within one, two or three years after the start of the follow-up (Models A3.1-A3.3), and (iv) for never smokers (Model A4). In these healthier sub-samples, it is less likely that an undiagnosed disease would be driving the weight change and confounding the weight change-mortality association. Models A1-A4 continue to control for changes in diagnosed conditions and in self-rated heath that take place during the weight change period. The results for these models are shown in eTable 2.

Results for Model A1, which excludes those with *any* diagnosed conditions at first interview, are closely in line with our main results (Model 2b, eTable 2), even though the sample size has dropped from 13,104 to 4,803 and number of deaths from 1,983 to 384. The effect of large weight loss continues to be associated with excess mortality if initial BMI is in the normal or overweight range, but at BMI = 30 the effect becomes weak. The difference with respect to Model A2 may be due to a much smaller sample size, as the statistical precision decreases with sample size. The estimated effects of small weight loss are also close to the ones estimated for the full sample, but less precisely estimated. This again may be due to the decrease in sample size (63 % in total sample size and 81 % in the number of deaths). For weight gains, large or small, the point estimates are also consistent with the ones obtained from the whole sample: there

is no evidence that small weight gains would be associated with increased mortality and there is weak evidence that large gains may potentially be associated with increased mortality among obese people.

Results for Model A2, which excludes those with anything less than good self-rated health at the first interview, are also consistent with our main results (Model 2b). The effects of large and small weight losses continue to be associated with excess mortality if initial BMI is in the normal or overweight range, although at BMI level 30 the effects become weak. The difference with respect to Model A2 may be due to a smaller sample size, as the number of deaths 43 % smaller (1,136 vs 1,983) than in Model 2b. For weight gains, large and small, the point estimates continue to be consistent with our main results (Model 2b).

In Models A3.1-A3.3, we exclude those who died within one, two or three years after the start of the follow-up (the second interview). Those who died within a short time may be more likely to have lost weight due to illness. The results of Models A3.1-A3.3 are in line with our main results (Model 2b). Large and small weight losses are associated with increased mortality among normal, overweight and obese people up to a BMI of 32-33 (exact calculations not shown). Large weight gains are not associated with increased mortality except if initial BMI is close to 35, and there is no evidence that small weight gains would be associated with increased mortality for any initial BMI.

Model A4, eTable 2, excludes current and former smokers. Again, the results are consistent with the results of Model 2b. Large and small weight losses are associated with increased mortality unless initial BMI is above ~32, large weight gains are associated with increased mortality only if initial BMI is close to 35, and small weight gains are not associated with increased mortality.

Second, if the initial weight distribution from which we start observing weight change is heavily driven by recent unobserved changes, our results may give a biased picture on the modifying effect of initial BMI in the weight change-mortality relationship. Consider, for example, a situation where persons who are normal weight (BMI 18.5-25) at the start of the weight change period had lost weight due to illness before entering the study. Then the effect of weight gain may reflect a process of recovery, potentially leading to an underestimation for the effect of weight gain on mortality. To study the robustness of our results to unobserved weight changes which took place prior to entering the study, we estimate the Model 2b for a sub-group of people whose weight remained stable (less than 1 BMI unit change) between the interviews 1 and 2 and estimate the effects of weight change between interviews 2 and 3, using the weight status at interview 2 as the initial weight status. eTable 2, Model A5 shows the results of this sensitivity test. The results of Models 2b and A5 are qualitatively consistent. For both models, large and small weight losses are associated with increased mortality until initial BMI is somewhere between 30 and 35. Thus the conclusion that weight losses are associated with increased mortality among normal weight, overweight, and mildly obese people do not change. Our conclusions concerning weight gains, based on Model 2b and other results shown in the manuscript were that small weight gains are not associated with increased mortality, and large weight gains are potentially associated with increased mortality, but only among obese people. The results for Model A5 are consistent with these conclusions. For large weight gains, the point estimates are in line with those obtained from Model 2b, although the estimates are less precise when compared to the main model (Model 2b). This decrease in accuracy, however, is likely to be a power issue because in Model A5 the sample size drops from 13,104 to 6,593 and number of deaths from 1,983 to 812. For small weight gains, the effects are consistent between Models

2b and A5. The small differences between Model 2b and Model A5 suggest that the estimated effects of weight change on mortality by initial BMI level are not seriously confounded by weight changes preceding the first weight measurement.

Third, we study the robustness of our results to potential over-adjustment. We estimate an additional model where we adjust for pre-existing diseases and self rated health in the first interview, but do not adjust for the *changes* that take place in health status during the weight change period. With respect to over-adjustment, controlling changes during the two year period when weight change is measured may constitute a larger problem than controlling for health status that precedes the weight change. Model A6, eTable 2 reports results for this model. The results of Model A6 are largely consistent with our main results (Model 2b), suggesting that large and small weight losses are associated with increased mortality at least up to initial BMI of 30; that large weight gains may be associated with excess mortality only among the obese; and that small weight gains are not associated with excess mortality. The magnitude of some of the effects, however, is larger with no adjustment for changes in health status. For large weight loss, for example, the estimated effect at initial BMI = 30 is 1.61 with full adjustment (Model 2b), and 1.77 when we do not adjust for changes in health status. For large weight gains, the effects are slightly larger at high initial BMI levels. For example, for initial BMI = 35 the effect is 1.45 for Model A6 and 1.33 for the fully adjusted Model 2b. These differences suggest that the fully adjusted model may underestimate some of the effects due to adjustment for variables that are on the causal pathway from weight change to death. The differences, however, are minor. Most importantly, the differences suggest that our main results may underestimate, rather than overestimate, the negative effects of weight loss. Thus over-adjustment is not likely to change

our conclusion that weight loss may increase mortality among overweight and potentially also among mildly obese people.

Fourth, we consider an alternative model specification for the interaction between weight change and initial BMI. In our main model (Model 2b), the interaction between weight change and initial BMI does not include higher order terms. Model A7 extends Model 2b by including an interaction between weight change and quadratic initial BMI in the model. The effect of weight change is then estimated as $\boldsymbol{\beta}'_1 + \boldsymbol{\beta}'_{12} BMI + \boldsymbol{\beta}'_{22} BMI^2$, where $\boldsymbol{\beta}'_1$ is the estimated direct effect of weight change (large weight loss, small weight loss, large weight gain, or small weight gain); $\boldsymbol{\beta}'_{12}$ is the estimated interaction effect between weight change and initial BMI; and $\boldsymbol{\beta}'_{22}$ is the estimated interaction effect between weight change and squared initial BMI. The results, shown in Model A7, are consistent with our main results (Model 2b).

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eTable 1. Baseline demographic and health characteristics at first interview for the analyzed sample, for those who were lost due to attrition before the second interview, and for those who were excluded because BMI change was 5 units or more. Health and Retirement Study, 50-70 Year Old Participants, 1992-2006.

	Analyzed sample (n = 13,104)		Attrition before the second interview (n = 808)		BMI change > 5 units between the first two interviews (n = 445)	
	Mean	Standard error	Mean	Standard error	Mean	Standard error
Age at first interview, years	56.9	4.89	57.5	4.70	56.7	4.62
Age at second interview, years	58.8	4.88	-	-	58.6	4.63
Died during the follow-up, %	15.1		-	-	25.8	
Age at death for those who died within the follow-up	66.7	5.69	-	-	65.2	5.99
Women, %	50.3		43.5		64.3	
Race/Ethnicity, %						
Non-Hispanic white	74.1		65.2		51.9	
Non-Hispanic black	15.4		19.7		27.0	
Hispanic	8.4		11.6		18.4	
Other	2.2		3.5		2.7	
Education, years	12.3	3.19	11.6	3.45	10.8	3.95
Current smoker, %	28.6		31.5		31.9	
Previous smoker, %	34.2		36.4		28.5	
Initial BMI	27.1	4.92	27.2	5.21	32.2	8.78
Self rated health §	3.4	1.18	2.9	1.13	2.8	1.26
Diagnosed conditions before entering the study, %						
High blood pressure or hypertension	34.4		43.1		49	
Diabetes or high blood sugar	9.5		13.9		20	
Cancer or a malignant tumor (not skin cancer)	4.9		10.7		6.7	
Chronic lung disease except asthma	4.8		10.1		6.7	
Heart attack, cor. heart disease, other heart problems	11.2		17.7		13.5	
Stroke or transient ischemic attack (TIA)	2.7		5.9		6.1	
Emotional, nervous, or psychiatric problems	7.3		10.8		11.5	
Arthritis or rheumatism	34.4		37		44.3	
No pre-existing conditions	36.7		26.6		23.6	

§ Measured on a scale from 5 (excellent) to 1 (poor)

† Measured on a scale from -4 (from excellent to poor) to +4 (from poor to excellent)

eTable 2. Effect of Two-Year Weight Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval by Model, Initial Body Mass Index (BMI) and Weight Change Category. Reference group stable weight. Health and Retirement Study, 50-70 Year Old Participants, 1992-2006.

Unless otherwise stated, all models control for initial BMI, squared initial BMI, sex, age, age squared, race/ethnicity, cohort, education, household income, physical activity, smoking, pre-existing conditions, changes in diagnosed conditions, initial self-rated health and changes in self-rated health.

Model 2b (The same model as Model 2b in the Manuscript): Full sample; weight change interacted with BMI.

N=13,104, Deaths=1,983

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	3.55	2.23, 5.66	1.35	1.07, 1.70	0.83	0.56, 1.24	0.95	0.76, 1.18
20	1.00	-	3.20	2.12, 4.85	1.32	1.13, 1.47	0.87	0.61, 1.24	0.94	0.77, 1.14
25	1.00	-	2.27	1.75, 2.95	1.25	1.13, 1.35	1.00	0.78, 1.29	0.91	0.80, 1.04
30	1.00	-	1.61	1.31, 1.98	1.19	1.06, 1.28	1.15	0.93, 1.43	0.88	0.77, 1.02
35	1.00	-	1.14	0.84, 1.55	1.12	0.95, 1.25	1.33	1.00, 1.77	0.85	0.69, 1.06
40	1.00	-	0.81	0.50, 1.30	1.06	0.88, 1.19	1.53	1.03, 2.29	0.83	0.61, 1.13

Model A1: As Model 2b, but sample reduced to those who did not have any diagnosed conditions at the first interview.

N=4,803, Deaths=384

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	3.71	1.43, 9.64	1.43	0.75 2.72	0.38	0.10, 1.43	0.57	0.20, 1.68
20	1.00	-	3.23	1.42, 7.38	1.35	0.78, 2.33	0.43	0.14, 1.33	0.70	0.33, 1.46
25	1.00	-	2.04	1.23, 3.40	1.12	0.83, 1.52	0.61	0.30, 1.21	0.85	0.54, 1.31
30	1.00	-	1.29	0.70, 2.38	0.93	0.62, 1.40	0.86	0.39, 1.89	1.02	0.78, 1.35
35	1.00	-	0.81	0.29, 2.25	0.77	0.37, 1.59	1.22	0.33, 4.51	1.24	0.79, 1.96
40	1.00	-	0.51	0.12, 2.28	0.64	0.22, 1.88	1.73	0.25, 12.02	1.32	0.77, 2.26

Model A2: As Model 2b, but sample reduced to those whose self-rated health was good, very good or excellent at the first interview.

N=10,270, Deaths=1,136

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	4.39	2.29, 8.41	1.55	1.11, 2.17	0.88	0.48, 1.58	0.89	0.64, 1.22
20	1.00	-	3.76	2.11, 6.68	1.49	1.11, 2.00	0.90	0.53, 1.53	0.89	0.68, 1.18
25	1.00	-	2.23	1.54, 3.24	1.30	1.09, 1.56	0.99	0.70, 1.41	0.91	0.76, 1.08
30	1.00	-	1.33	0.96, 1.84	1.14	0.95, 1.37	1.09	0.78, 1.54	0.93	0.76, 1.13
35	1.00	-	0.79	0.48, 1.29	1.00	0.75, 1.34	1.20	0.73, 1.99	0.94	0.68, 1.31
40	1.00	-	0.47	0.23, 0.97	0.87	0.57, 1.35	1.32	0.64, 2.74	0.96	0.59, 1.55

eTable 2 (continued) Effect of Two-Year Weight Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval by Model, Initial Body Mass Index (BMI) and Weight Change Category. Reference group stable weight. Health and Retirement Study, 50-70 Year Old Participants, 1992-2006.

Unless otherwise stated, all models control for initial BMI, squared initial BMI, sex, age, age squared, race/ethnicity, cohort, education, household income, physical activity, smoking, pre-existing conditions, changes in diagnosed conditions, initial self-rated health and changes in self-rated health

Model A3.1: As Model 2b, but excludes those who died within a year after the start of the follow-up (second interview).

N=12,897 Deaths=1,840

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	2.67	1.59, 4.49	1.25	0.93, 1.68	0.77	0.50, 1.17	0.96	0.76, 1.21
20	1.00	-	2.49	1.56, 3.95	1.23	1.01, 1.50	0.80	0.55, 1.18	0.95	0.78, 1.17
25	1.00	-	1.95	1.45, 2.62	1.21	1.06, 1.38	0.95	0.73, 1.25	0.92	0.80, 1.05
30	1.00	-	1.53	1.22, 1.91	1.18	1.03, 1.36	1.13	0.90, 1.41	0.89	0.77, 1.03
35	1.00	-	1.20	0.88, 1.63	1.16	0.94, 1.45	1.33	0.99, 1.79	0.86	0.68, 1.07
40	1.00	-	0.94	0.58, 1.52	1.16	0.91, 1.48	1.57	1.04, 2.39	0.83	0.60, 1.14

Model A3.2: As Model 2b, but excludes those who died within two years after the start of the follow-up (second interview).

N=12,729 Deaths=1,716

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	2.29	1.29, 4.06	1.32	0.97, 1.78	0.77	0.49, 1.19	0.92	0.72, 1.17
20	1.00	-	2.15	1.29, 3.59	1.27	1.03, 1.55	0.81	0.54, 1.21	0.92	0.74, 1.14
25	1.00	-	1.75	1.25, 2.43	1.22	1.06, 1.39	0.97	0.73, 1.28	0.91	0.79, 1.05
30	1.00	-	1.42	1.11, 1.80	1.17	1.01, 1.35	1.16	0.91, 1.46	0.90	0.78, 1.05
35	1.00	-	1.15	0.83, 1.60	1.12	0.89, 1.40	1.38	1.02, 1.87	0.90	0.71, 1.13
40	1.00	-	0.93	0.56, 1.55	1.11	0.86, 1.43	1.65	1.07, 2.56	0.89	0.64, 1.24

Model A3.3: As Model 2b, but excludes those who died within three years after the start of the follow-up (second interview).

N=12,503 Deaths=1,555

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	2.51	1.33, 4.73	1.24	0.90, 1.70	0.71	0.43, 1.15	0.98	0.76, 1.26
20	1.00	-	2.31	1.31, 4.06	1.23	1.00, 1.53	0.74	0.48, 1.16	0.97	0.77, 1.21
25	1.00	-	1.74	1.21, 2.49	1.23	1.07, 1.42	0.89	0.65, 1.20	0.94	0.81, 1.09
30	1.00	-	1.31	1.01, 1.70	1.23	1.06, 1.43	1.06	0.82, 1.36	0.91	0.78, 1.06
35	1.00	-	0.99	0.69, 1.42	1.23	0.97, 1.56	1.26	0.91, 1.75	0.88	0.69, 1.11
40	1.00	-	0.75	0.42, 1.32	1.23	0.94, 1.60	1.50	0.93, 2.40	0.85	0.60, 1.20

eTable 2 (continued) Effect of Two-Year Weight Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval by Model, Initial Body Mass Index (BMI) and Weight Change Category. Reference group stable weight. Health and Retirement Study, 50-70 Year Old Participants, 1992-2006.

Unless otherwise stated, all models control for initial BMI, squared initial BMI, sex, age, age squared, race/ethnicity, cohort, education, household income, physical activity, smoking, pre-existing conditions, changes in diagnosed conditions, initial self-rated health and changes in self-rated health

Model A4: As Model 2b, but excludes current and former smokers.

N=4,867, Deaths=434

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	3.80	1.45, 9.92	1.50	0.83, 2.71	0.72	0.31, 1.68	0.88	0.54, 1.45
20	1.00	-	3.45	1.46, 8.16	1.45	0.86, 2.46	0.79	0.36, 1.73	0.88	0.57, 1.37
25	1.00	-	2.50	1.43, 4.38	1.31	0.93, 1.83	1.08	0.61, 1.94	0.89	0.66, 1.19
30	1.00	-	1.81	1.22, 2.7	1.18	0.89, 1.55	1.48	0.94, 2.34	0.89	0.67, 1.18
35	1.00	-	1.32	0.78, 2.21	1.06	0.71, 1.58	2.03	1.28, 3.24	0.89	0.59, 1.34
40	1.00	-	0.95	0.43, 2.14	0.95	0.52, 1.75	2.79	1.52, 5.10	0.90	0.50, 1.62

Model A5: As Model 2b, but sample reduced to those who had stable weight between interviews 1 and 2. Weight change and other control variables are measured from interviews 2 and 3

N=6,593, Deaths=812

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	3.20	1.64, 6.25	2.32	1.54, 3.52	0.85	0.4, 1.81	1.16	0.8, 1.67
20	1.00	-	2.97	1.63, 5.42	2.17	1.52, 3.10	1.01	0.59, 1.71	1.16	0.84, 1.59
25	1.00	-	2.30	1.53, 3.47	1.73	1.41, 2.13	1.19	0.8, 1.77	1.15	0.95, 1.4
30	1.00	-	1.78	1.29, 2.46	1.38	1.08, 1.76	1.41	0.91, 2.19	1.15	0.9, 1.47
35	1.00	-	1.38	0.91, 2.09	1.10	0.72, 1.67	1.67	0.89, 3.12	1.15	0.77, 1.73
40	1.00	-	1.07	0.58, 1.97	0.88	0.47, 1.64	1.75	0.88, 3.52	1.15	0.63, 2.09

Model A6: As Model 2b, but does not adjust for changes in self-rated health or diagnosed diseases between the first and second interviews. The model does adjust for self-rated health and diagnosed diseases at the first interview.

N=13,104, Deaths=1,983

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	4.10	2.55, 6.60	1.26	1.00, 1.59	0.91	0.61, 1.34	0.94	0.75, 1.17
20	1.00	-	3.67	2.41, 5.60	1.26	1.02, 1.55	0.94	0.66, 1.34	0.93	0.77, 1.13
25	1.00	-	2.55	1.96, 3.32	1.24	1.09, 1.42	1.09	0.85, 1.40	0.92	0.80, 1.04
30	1.00	-	1.77	1.44, 2.18	1.23	1.08, 1.40	1.25	1.01, 1.56	0.90	0.78, 1.04
35	1.00	-	1.23	0.90, 1.68	1.22	0.99, 1.49	1.45	1.09, 1.91	0.88	0.71, 1.09
40	1.00	-	0.85	0.52, 1.38	1.21	0.91, 1.60	1.67	1.12, 2.48	0.87	0.64, 1.18

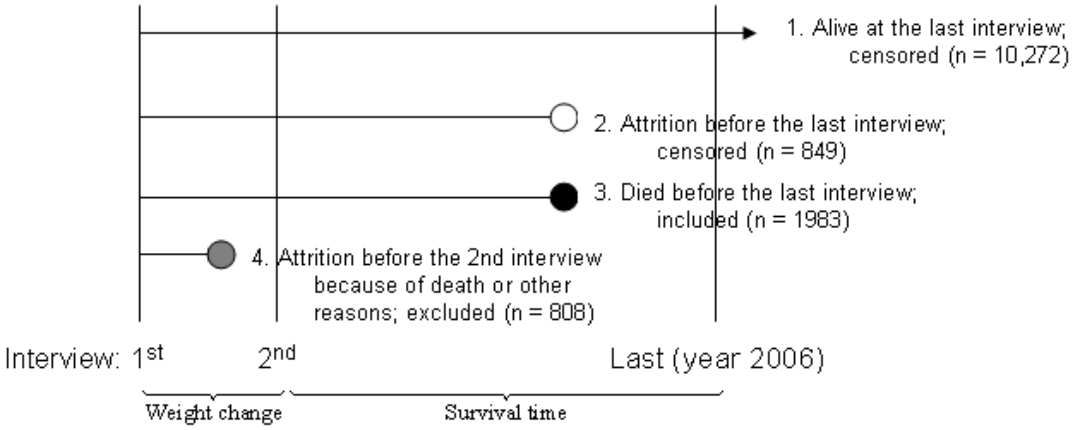
eTable 2 (continued) Effect of Two-Year Weight Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval by Model, Initial Body Mass Index (BMI) and Weight Change Category. Reference group stable weight. Health and Retirement Study, 50-70 Year Old Participants, 1992-2006.

Unless otherwise stated, all models control for initial BMI, squared initial BMI, sex, age, age squared, race/ethnicity, cohort, education, household income, physical activity, smoking, pre-existing conditions, changes in diagnosed conditions, initial self-rated health and changes in self-rated health.

Model S7: As Model 2b, but includes quadratic BMI interacted with weight change in addition to the interaction between linear BMI and weight change.

N=13,104, Deaths=1,983

	Stable: change < 1 BMI units (Ref)		Large weight loss: 3-5 BMI units		Small weight loss: 1-2.9 BMI units		Large weight gain: 3-5 BMI units		Small weight gain: 1-2.9 BMI units	
Initial BMI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
18.5	1.00	-	3.11	1.75, 5.54	1.65	1.21, 2.24	1.05	0.67, 1.64	0.78	0.58, 1.05
20	1.00	-	2.77	1.75, 4.37	1.41	1.14, 1.76	1.03	0.72, 1.48	0.83	0.66, 1.05
25	1.00	-	1.96	1.58, 2.44	1.25	1.07, 1.47	1.02	0.83, 1.26	0.98	0.86, 1.11
30	1.00	-	1.51	1.20, 1.90	1.15	1.01, 1.31	1.11	0.87, 1.40	1.09	0.92, 1.28
35	1.00	-	1.26	0.94, 1.70	1.10	0.85, 1.41	1.30	0.96, 1.76	1.14	0.91, 1.44
40	1.00	-	1.14	0.76, 1.72	1.09	0.79, 1.50	1.65	1.13, 2.40	1.14	0.81, 1.61



eFigure 1. Time ordering of events for four hypothetical subjects. Weight change is measured between the first two interviews, and survival time is measured starting from the second interview. Those who exited the study before the second interview (808 subjects) are excluded from the study because key independent variable, weight change, is not observed.