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Modeling Obesity Histories in Cohort Analyses of Health and Mortality

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Abstract

There is great interest in understanding the role of weight dynamics over the life cycle in predicting the incidence of disease and death. Beginning with a Medline search, we identify, classify and evaluate the major approaches that have been used to study these dynamics. We identify four types of models: additive models, duration-of-obesity models, additive-weight-change models, and interactive models. We develop a framework that integrates the major approaches and shows that they are often nested in one another, a property that facilitates statistical comparisons.

Our criteria for evaluating models are two-fold: the model's interpretability and its ability to account for observed variation in health outcomes. We apply two sets of nested models to data on adults aged 50-74 years at baseline in two national probability samples drawn from NHANES. One set of models treats obesity as a dichotomous variable and the other treats it as a continuous variable. In three out of four applications, a fully interactive model does not add significant explanatory power to the simple additive model. In all four applications, little explanatory power is lost by simplifying the additive model to a duration model in which the coefficients of weight at different ages are set equal to one another. Other versions of a duration-of-obesity model also perform well, underscoring the importance of obesity at early adult ages for mortality at older ages.

Obesity is associated with a variety of adverse health conditions. Like many other risk factors for chronic disease, its effects are realized over an extended period of time. Interest in mapping the dynamics of obesity and health has grown as obesity has increased in nearly all parts of the world.¹

In this paper, we identify, classify and evaluate the major approaches that have been used to examine obesity/health linkages when they are studied as processes developing over time, and we propose a statistical framework for model selection. We consider models for analyzing the impact of obesity on health and mortality when observations are available on body mass index (BMI) at least twice in the adult lifetimes of cohorts in prospective studies.

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Our criteria for evaluating models are two-fold: the model's interpretability and its ability to account for observed variation in health outcomes. Using two national data sets, we contrast the results obtained by some of the major approaches and illustrate their varied interpretations.

Search Strategy

To identify approaches that have been used to study the dynamic relation between obesity and health outcomes, we conducted a systematic literature review using Medline (via PubMed) for the period 1950 through January 2012; details of the search criteria are included in the eAppendix. We sought prospective cohort studies in which the outcome of interest was the incidence of death or a condition associated with diabetes or coronary heart disease, and in which observations on BMI were available at least twice in the lifetime of cohorts prior to the measurement of incident death or disease. The search returned 1650 references. Title and abstract review yielded 110 articles for in-depth examination. We additionally performed searches based on reference lists of articles identified through the search, including those in review articles. Because of differences in biologic processes and in the types of measures used, we excluded articles focused primarily on weight at birth or in early childhood. We also excluded cross-sectional and case-control studies and review articles. We accepted articles regardless of whether BMI was measured or self-reported, whether it was reported retrospectively or contemporaneously, and whether other variables were absent or present. Altogether, 57 articles met our criteria.

Types of Models

We identify four types of models that have been employed in the literature: strictly additive models, duration-of-obesity models, additive-weight-change models, and interactive models. This list ranges roughly from the simplest to the most complex, and we treat them in this order. Some studies employ multiple approaches. We have assigned them to the most complex rubric that is appropriate, but have also included them elsewhere if there is some lesson to be learned from such an application.

We use the term “observations of BMI” to mean instances in the life course at which information on BMI is available. The observations may be in the form of BMI estimated at particular ages or at particular lengths of time before the period of exposure to the hazard begins. We treat the observations as independent of one another. To simplify the exposition, we express the models as though only two BMI observations are available, although the studies referred to may contain more than two observations of BMI.

Strictly additive models

These models have at base a construction of the form

$$H(x)=f [A+B_1O_1+B_2O_2], \quad (1)$$

where $H(x)$ is the rate of occurrence (or hazard) of an adverse health event at age x , A is a constant term, O_1 is BMI observed at time (or age) 1, and O_2 is BMI observed at a later time (or older age) 2. O_1 and O_2 may be dichotomous, i.e., function as an indicator of whether someone is obese or not, or consist of multiple categories. O_1 and O_2 may also be continuous variables indicating the distance of BMI above some threshold such as a BMI of 25 or 30. B_1 and B_2 indicate the effect on the outcome of a one-unit change in O_1 and O_2 , respectively. Equation (1) may be considered a generalized linear model.² Our focus is on

specifying the linear predictor in such a model, rather than the probability distribution of the dependent variable or the function that links the linear predictor with the hazard.³

The strictly additive models treat the obesity observations as two independent, additive variables.⁴⁻¹⁰ The typical underlying hypothesis, whether explicit or not, is that obesity is damaging to subsequent health whenever it occurs, so that B_1 and B_2 are both expected to be positive. This assumption is entirely plausible. Comparison of the B 's enables an estimate to be made of the relative importance of obesity at different ages or lengths of time before baseline. We believe that identifying the relative importance of BMI at different ages has been a central concern of life cycle models of obesity. The simple additive model makes this identification in a straightforward manner.

However, the relative values of B_1 and B_2 are also subject to measurement error in O_1 and O_2 . Measurement errors that are randomly distributed about a mean of zero have the effect of biasing coefficients towards zero.¹¹ Measurement error is a special threat when O_1 is measured retrospectively.¹² The relative size of B_1 and B_2 may also be affected by whether the value of obesity indicated by O_2 is sustained over a longer or shorter period than that indicated by O_1 . If O_2 is on the causal pathway between O_1 and the outcome variable, the coefficient on O_1 may be biased downwards by the so-called “reversal paradox”.¹³

Duration of obesity models

The most basic of these models takes the form of

$$H(x) = f [A + B_3 D], \quad (2)$$

where D is the estimated duration of obesity between observations 1 and 2. Mishra et. al¹⁴ refer to such a model as an “accumulation model.” A duration model shares with an additive model the reasonable assumption that obesity is damaging whenever it occurs. It makes the additional assumption that the effect of obesity does not depend on when in the life cycle it occurs.

Duration can be estimated in different ways. When obesity is treated as a binary variable, one can observe whether someone is obese at times 1 and 2 and assume that each of the obesity values applies to one-half of the period between time 1 and time 2. One pair of duration studies requires that an individual be obese at both ages 1 and 2 in order that this interval be added to the duration of obesity.^{15,16} Giving equal weight to O_1 and O_2 assumes that obesity levels at different ages, or lengths of time before baseline, have the same effect on the outcome, i.e., that B_1 and B_2 are identical.

An alternative way of calculating the duration of obesity is to observe BMI values at t_1 and t_2 and assume that BMI changes linearly between these times; see below for an application. One can then use the fitted function to estimate the proportion of the interval spent above the obesity-defining value of BMI. If more than two observations of BMI are available, then more complex functions can be fitted. Several other variants of duration variables have been used. In one study the researchers have calculated duration of obesity by subtracting the age at which someone was first observed as obese from age at baseline, without attention to weight histories after obesity was first attained.¹⁷ A potential advantage of this formulation is that the measure is robust to illness-induced weight loss, including that associated with obesity itself. Another study combined the estimated duration of obesity with the observed distance above an optimal weight to form a combination intensity/duration variable equivalent to pack-years in the analysis of smoking.¹⁸

Some studies^{19,20} create a variable representing the average level of obesity at various observations (i.e., dividing the sum of O_1 and O_2 by 2). Such a model is algebraically indistinguishable from a duration model when the duration variable is a linear transformation of the mean of O_1 and O_2 .

Additive weight change models

Many life cycle models that investigate the impact of obesity on health include a weight-change term. The most basic of these models²¹⁻²⁴ takes the form of

$$H(x) = f[A + B_4(O_2 - O_1)] \quad (3)$$

Additive weight-change models implicitly assume that the coefficients of O_1 and O_2 are equal but opposite in sign. The implausibility of this assumption is not usually recognized. The hypothesis underlying most weight-gain studies is that weight gain has an adverse effect on health (i.e., B_4 is positive). If B_4 is positive, then the implication is that obesity at the earlier age is protective, i.e., it is negatively related to the hazard being investigated. If B_1 and B_2 are both positive in Model 1, then the differencing of BMI in the weight gain model can result in small and insignificant coefficient on weight change itself.^{24,25}

The effects of weight loss can be studied using the same analytic design that is used in studies of weight gain.²⁶⁻²⁹ Weight-loss models often differentiate between intentional and unintentional weight loss.³⁰⁻³² The typical hypothesis in intentional weight-loss models, consistent with weight-gain models, is that weight loss is advantageous, i.e., that B_4 is positive. On the other hand, unintentional weight loss is expected to be associated with higher mortality, usually because it is indicative of an underlying medical condition that is producing the loss (i.e., B_4 is negative, implying that obesity at the most recent observation is protective). When it is serving only as an indicator of an unobserved medical condition, unintentional weight loss should be treated in a latent variable model rather than used directly in a regression equation. It should be noted that the distinction between intentional and unintentional weight loss does not precisely distinguish between underlying motivations because many who are intentionally losing weight are doing so because of a medical condition.³³

In addition to $(O_2 - O_1)$, either O_1 or O_2 itself is often added to the model.^{9,22,28,29,32,34,35-42} If O_1 is added, the model becomes

$$H(x) = f[A + B_5 O_1 + B_6(O_2 - O_1)]. \quad (3A)$$

This model is simply a reparameterization of Model 1.^{13,43} B_1 will be equal to $(B_5 - B_6)$ and B_2 will be equal to B_6 . Thus, the coefficients of Model 1 can be obtained, in a roundabout way, by a proper interpretation of the coefficients in 3A. Relative to Model 1, no new information is obtained by expressing one of the two BMI-based variables as a weight-change variable. The interpretation of equation 3A can be awkward. For example, if one imagines that $(O_2 - O_1)$ is fixed, then B_5 will indicate not only the effect of changes in O_1 but also of simultaneous changes of equal magnitude occurring in O_2 .

If O_2 is added to weight change rather than O_1 , the model becomes

$$H(x) = f[A + B_7 O_2 + B_8(O_2 - O_1)]. \quad (3B)$$

Once again, model 3B is a reparameterization of (1), where $B_1 = -B_8$ and $B_2 = (B_7 + B_8)$. While it is tempting to compare the coefficients of 3A and 3B in order to infer whether a “prospective” or a “retrospective” approach is better suited to studying the effects of obesity,³⁶ it must be recognized that the question cannot be answered by such a comparison; the models are equivalent.

Measurement error in O_1 produces a negative correlation between O_1 and the change variable. Measurement error in O_2 produces a positive correlation between O_2 and the change variable. These correlations produce multicollinearity among independent variables when either O_1 or O_2 are in a regression that includes the change variable, which increases standard errors of coefficients.

Interactive models

Interactive models investigate the possibility that obesity levels recorded at two or more points in time are interactive in their effects, i.e., are subject to effect modification.^{9,25,27,33,44-65} A basic interactive model is

$$H(x) = f [A + B_9 O_1 + B_{10} O_2 + B_{11} O_1 O_2] \quad (4)$$

In this model, B_{11} represents the interaction between the effects of O_1 and O_2 . A positive value of B_{11} indicates that the effect of O_2 is greater at higher values of O_1 , and vice versa. Interactive models are the most general of the types considered here; models of Types I-III can be thought of as simplifications of interactive models that exclude the interaction terms.

Weight change variables figure heavily in interactive models, including variables representing the intentionality of weight loss.^{30,66,67} One common approach is to examine whether the impact of weight change varies across initial (or baseline) weight categories. By not including initial (or baseline) weight *additively* in the model, such an approach avoids being isomorphic with models of Type I. Use of a simple linear weight change variable that is interacted with initial BMI is a sensible expedient that allows for possibilities that cannot be examined in an additive model.

Studies of weight cycling or fluctuation *per se* are a special type of interactive model that typically involves three or more observations on BMI.^{52,59,62} Categorical variables are typically constructed that identify people who have moved both up and down in BMI during different segments of their life histories. Intentionality of weight loss is readily integrated into weight cycling models.^{33,60,65-67} One study used principal components analysis to identify a component of attained weight, a second component of weight gain or loss, and additional components of weight cycling.⁶⁴

Statistical Considerations in Model Selection

Few of the papers considered here are overtly reflective about model selection; most simply present a model, or several models, and estimate their parameters. Parameter estimation is the central statistical concern, rather than explaining variance in outcomes. The choice of a model may be driven by biologic plausibility, although it typically is not justified in those terms.

When attention is shifted to model selection, the amount of variance explained by different models becomes a useful criterion for evaluating the models. The majority of studies in the obesity literature use hazard, or Cox, models. Criteria for comparing hazard models depend on whether or not the models are “nested”. Any two models are nested as long as the set of parameters estimated in the more restrictive model (i.e., with fewer free parameters) is a

subset of the parameters estimated in the less restrictive model (with more free parameters).⁶⁸ When linear models are nested, the significance of differences in their relative explanatory powers can be examined using the F-test.⁶⁹ On the other hand, the criteria for selecting among non-nested hazard models are not settled.⁷⁰

Fortunately, all four of the model types identified above can be treated in such a way that they are nested. Interactive models of Type IV are generally the least restrictive. Simple additivity can be tested by using an F-test to compare the variance explained by Model 1 to that of Model 4. A duration model can be tested relative to the additive model by examining whether the effects of obesity at t_1 and t_2 are comparable in their effects, i.e., whether significant explanatory power is lost by assuming that B_1 is equal to B_2 . A simple weight-change model can be investigated relative to a simple additive model by constraining B_1 and B_2 to be equal but opposite in sign. Models 3A and 3B, on the other hand, will explain the same amount of variance as Model 1. The choice between these models is a matter of indifference from the viewpoint of explaining variance, but not from the viewpoint of interpreting results.

Below, we estimate and evaluate the various model types on two datasets each of which has three observations of BMI. We use both dichotomous and continuous measures of BMI.

Methods

We examine adults aged 50-74 at baseline. The first sample is constructed by pooling the National Health and Nutrition Examination Survey NHANES 3 (1988-1994) and NHANES 1999-2004 continuous waves. NHANES 3 and NHANES 1999-2004 are independent cross-sectional surveys. For simplicity, we refer to this first sample as NHANES. Information on body weight is available at baseline, at age 25 years, and 10 years prior to baseline (pertaining to an average age of 50.9). Weight at age 25 and 10 years prior to baseline are reported retrospectively. BMI is calculated by combining the relevant weight observation with self-reported height at baseline. We use self-reports of weight at baseline.

A second sample is the 1982-1984 NHANES I Epidemiological Follow-up Survey (NHEFS), which is a longitudinal follow-up survey of NHANES I (1971-1975). The NHEFS contains retrospective reports of weight at ages 25 and 40 years in addition to weight at baseline. The NHEFS does not contain data on height. We use measured height when the respondents were surveyed in NHANES I (1971-1975).

Cox proportional hazard models are used to estimate how mortality risks vary with BMI. Respondents enter the risk set two years after they are surveyed, a delay designed to reduce potential confounding from illness-related weight loss. All models include variables representing age at baseline, sex, race/ethnicity (3 categories), educational attainment (5 categories) and smoking status at baseline (current, former, never). NCHS-supplied survey weights and design elements (strata and primary sampling units) are used. Information on deaths is available through 31 December 2006 for NHANES and through 31 December 1992 for NHEFS. There were 1,815 deaths (of 8,907 respondents) in NHANES and 625 deaths (of 4,150 respondents) in NHEFS.

As noted above, duration models can be estimated in several ways. A straightforward duration model is one that is nested within the simple additive model (i.e., Model 1), where B_1 is constrained to be equal to B_2 . In addition to estimating this type of duration model, we constructed four alternative duration variables. Each of these was calculated by assuming that BMI changed linearly between adjacent BMI observations. The first variable estimates the total years beyond age 25 spent at or above a BMI of 30.0. It is coded 0 for those who

did not have a BMI>30 on any of the three occasions. The second calculates the *percentage* of time between age 25 and baseline age spent above a BMI of 30.0. The third measures the number of years since first becoming obese. This variable is calculated by subtracting the age at which someone first becomes obese from baseline age. Respondents who were obese at age 25 were given a value of baseline age minus 25. A fourth variable combines both duration and intensity of obesity, which we refer to as BMI-years. It measures the area under the BMI line and above a BMI of 30.0.

Results

Models Based on a Binary Measure of Obesity

Table 1 provides basic descriptive characteristics of the samples. Note that, for purposes of obtaining a sufficient sample size, we have defined the cut-off for obesity at age 25 years at a BMI of 25. We begin with results from models treating BMI as a binary 0/1 variable.¹⁴ Table 2 shows the interactive binary model, which is akin to Model 4 but for the case of three observations. This model is termed “saturated” because it distinguishes the effects of all eight (2x2x2) trajectories of obesity histories. We use a reference category of (0,0,0), representing people who were never obese. Relative to this category, those who were always obese (1,1,1) had an excess mortality of 69% in NHANES and 116% in NHEFS. However, in NHANES, the highest risk of mortality is observed for (1,1,0) and (0,1,0), groups that lost weight in the most recent interval.

Table 3 shows the estimated additive, duration, and weight-change models for the binary case. As indicated above, these models are nested within the saturated interactive model so that we can use F-tests to examine whether there is statistical evidence to reject various restrictions relative to the saturated model. Results for the strictly additive model in Table 3 show that, in both samples, weight at age 25 (O_1) is the only observation significantly associated with mortality. In NHANES, the F-test comparing the additive to the fully saturated model is significant ($P = 0.0111$), indicating that the inclusion of interaction terms contributes significantly to the explanatory power of the model. In NHEFS, the addition of interactive terms did not significantly improve upon the additive model.

A duration model with the further restriction that $B_1=B_2=B_3$ is nested within the additive model as well as within the fully saturated model. The duration variable can take on values between 0 and 3 depending on the frequency with which someone is observed to be obese. The hazard ratios are similar in both datasets and indicate that one additional instance of obesity increases risks by 19%-26%. When this duration model is tested against the additive model, the F-tests indicate that the additive model does not add significant explanatory power to the simpler duration model (P -values for the F-tests are greater than 0.05).

Table 3 also presents the results of using Model IIIA. Because this model is just an alternative parameterization of the simple additive model, the P -values of the two models are identical. The coefficient of O_1 differs in the additive and weight change models because, in the weight change model, O_1 appears twice, in O_1 itself and in (O_2-O_1) . The actual coefficient of O_1 in the additive model (e.g., 1.26 in NHANES) can be recovered in a circuitous way from the weight change model by dividing the hazard ratio of O_1 by the hazard ratio of (O_2-O_1) : $1.71/1.36 = 1.26$. Similarly, the coefficient of O_2 in the simple weight-change model can be recovered by dividing the hazard ratio of (O_2-O_1) by the hazard ratio of (O_3-O_2) : $1.36/1.09 = 1.25$.

Models Based on a Continuous Measure of Obesity

Binary models are primitive because they employ only two weight categories. But using additional weight categories can create complexity in tracking weight histories. For example, three observations with five weight categories produce 125 combinations of weight histories to be investigated. An attractive alternative is to use a continuous model. Continuous models use more detailed information about a person's BMI but do not require large numbers of variables. One straightforward continuous model requires no more variables than the binary model because it uses a variable that indicates not simply whether someone is obese but how far above the obesity-defining threshold she is. We use the standard BMI threshold of 30 for all BMI observations. Someone with a BMI of 30 or less has a value of zero on this variable, while someone above 30 has a value of $(\text{BMI} - 30)$. Using this variable linearly in a hazard model implies that risks increase exponentially above a BMI of 30 (i.e., they increase linearly in the log of the hazard). Strong empirical support for such a shape emerged from a collaborative analysis of 57 prospective studies.⁷¹

Table 4 shows results from a fully interactive model treating BMI continuously. None of these interactive variables has a significant coefficient in Table 4. Thus, it is not surprising in Table 5 that there is no significant gain in explanatory power from adding the interactive terms to the additive model. In the NHANES dataset the coefficients of O_1 , O_2 , and O_3 are nearly identical. As a result, the duration model works exceptionally well and nothing significant is gained by distinguishing among the times at which someone is obese (i.e., using the additive model). On grounds of parsimony, the duration model is superior to the additive model in NHEFS as well.

It would be tempting, but incorrect, to conclude from the parameters of Model IIIA in Table 5 that the effect of O_1 is large and significant; each one-unit increment of BMI at age 25 in the weight change model raises mortality by 13.8% in NHEFS and 8.2% in NHANES. However, the actual effect of O_1 can be recovered in NHANES as $1.082/1.055=1.026$.

The final model in Table 5 differentiates the effect of weight loss and weight gain in the two intervals. This model is not nested with respect to the other models so we cannot test its relative explanatory power with an F-test. This model indicates that both gaining weight and losing weight are associated with higher mortality. The interpretation of this model is even more arduous than that of the additive weight gain model, with each of O_1 , O_2 and O_3 appearing multiple times. In each case, an observed weight contributes both positively and negatively to one of the weight-change variables. Under conventional hypotheses that associate obesity with increased risk of disease and death, one would expect weight loss to have a protective effect. That this effect does not appear in Table 5 indicates that other mechanisms, perhaps related to illness, may be at work.

Table 6 shows the results of using the alternative duration variables that were described above. These models are not nested in an additive model. All of these duration variables are highly predictive of death. The first variable, which uses linear interpolation to estimate the number of years someone was obese above age 25, shows that each additional year of obesity raises mortality by about 1.5%. This finding is consistent across the two datasets. The second variable, the proportion of the interval spent obese, also shows highly consistent results across the data sets.

The ratio of a coefficient to its standard error, the t-statistic, is quite similar for these four variables within each data set. Such a result is not surprising because the variables are highly correlated with one another. For example, the "years since first becoming obese" is correlated with the total number of years obese at 0.95-0.96 in the two data sets. The similarity of results discourages any effort to choose among these variables. We simply

conclude that all of the duration of obesity measures are highly predictive of death in these data sets and deserve consideration in other lifecycle models of obesity's effects.

Summary and Conclusion

We have developed a framework that integrates the major approaches to studying the effects of obesity over the life cycle on health outcomes. Among the models that we have considered, additive weight-change models are most difficult to interpret. The challenge to interpretation results from the fact that weight measured at a particular age usually appears twice in such models, once with a positive sign and once with a negative sign. The additive weight change model is simply an alternative parameterization of a simpler and more straightforward additive model. More complex weight-change models may avoid isomorphism with strictly additive models, but they still require weight recorded at a particular age to appear with both positive and negative signs.

Ideally, choosing models on the basis of their explanatory power would be an empirical question that is addressed in each application. The choice among models is facilitated if the models are nested in one another. We have applied two sets of nested models to data from two national probability samples, one treating obesity as a binary variable and the other as a continuous variable. With the exception of the binary NHANES model, the fully interactive model did not add significant explanatory power to the simple additive model.

One result is consistent across the four combinations of obesity measures and data sets: simplifying the additive model to a duration model in which the coefficients of weight at different ages are set equal to one another does not entail a significant sacrifice of explanatory power. Thus, the duration model is preferred to the additive model in all cases. This result suggests that adult obesity is roughly equally damaging at whatever age it occurs. Such a potentially important result needs to be replicated in other data sets using comparable methods.

The attractiveness of duration models is underscored by the results of using four additional versions of a duration measure. These measures, which are based on linear interpolation, are all strongly predictive of death in both data sets. While models using these variables are not nested in other models, they are closely related to the nested duration models and gain appeal from the strong performance of the latter.

The predictive success of all of our duration models suggests that obesity in early adulthood is an important risk factor for mortality above age 50. Such results imply that, even if the upsurge in obesity prevalence were suddenly reversed, considerable damage has already been done among younger cohorts. Increased attention should clearly be placed on reducing the incidence of obesity at young adult ages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Descriptive Characteristics of the Samples Used

<i>Characteristic</i>	<i>NHANES^a</i>	<i>NHEFS^a</i>
<i>Baseline BMI; proportion (95% CI)</i>		
Underweight (<18.5 kg/m ²)	0.01 (0.01-0.01)	0.02 (0.01-0.02)
Normal (18.5-24.9)	0.32 (0.31-0.34)	0.39 (0.37-0.41)
Overweight (25.0-29.9)	0.39 (0.37-0.40)	0.40 (0.38-0.42)
Obese (30.0+)	0.28 (0.26-0.29)	0.20 (0.18-0.21)
<i>Middle-Age BMI^b; proportion (95% CI)</i>		
Underweight (<18.5)	0.02 (0.01-0.02)	0.02 (0.02-0.03)
Normal (18.5-24.9)	0.43 (0.41-0.44)	0.58 (0.56-0.60)
Overweight (25.0-29.9)	0.38 (0.37-0.39)	0.30 (0.29-0.32)
Obese (30.0+)	0.17 (0.16-0.18)	0.09 (0.08-0.10)
<i>Age-25 BMI; proportion (95% CI)</i>		
Underweight (<18.5)	0.08 (0.07-0.09)	0.07 (0.06-0.08)
Normal (18.5-24.9)	0.69 (0.68-0.70)	0.73 (0.71-0.74)
Overweight (25.0-29.9)	0.19 (0.18-0.20)	0.16 (0.15-0.18)
Obese (30.0+)	0.04 (0.04-0.05)	0.04 (0.03-0.05)
Obesity Duration (years); mean (95% CI)	4.46 (4.17-4.74)	3.47 (3.17-3.77)
Years Since Becoming Obese ^c ; mean (95% CI)	15.17 (14.44-15.91)	17.59 (16.69-18.49)
BMI-Years above BMI of 30.0; mean (95% CI)	18.65 (16.47- 20.83)	11.40 (9.92- 12.89)
Sample Size (No.)	8,907	4,150
Mortality follow-up	1988-2006	1982-1992
Person-years of follow-up	62,134	27,857
No. deaths	1,815	625

Notes: Ages 50-74 at baseline. Data shown are weighted except for sample size, person-years of follow-up, and number of deaths.

^aNHANES is a pooled sample of NHANES 3 (1988-1994) and NHANES 1999-2004. NHEFS refers to NHEFS 1982-1984.

^bRecall measure for age 40 in NHEFS and 10 years prior to baseline in NHANES (mean age of 50.9 years).

^cAmong those who were obese on at least one occasion.

Table 2
Saturated Binary Model Predicting Death from Any Cause

<i>Characteristic</i>	NHANES		NHEFS		NHANES	NHEFS
	HR (95% CI)		HR (95% CI)		%	%
<i>Stable</i>						
(0,0,0) ^a					57.2	67.3
(1,1,1)	1.69	(1.36-2.10)	2.16	(1.46-3.19)	8.9	5.2
<i>Gain</i>						
(0,1,1)	1.06	(0.79-1.40)	1.30	(0.52-3.27)	5.7	1.7
(0,0,1)	1.36	(0.97-1.91)	1.04	(0.70-1.56)	9.9	9.5
<i>Loss</i>						
(1,0,0)	1.26	(1.05-1.50)	1.55	(1.15-2.10)	9.1	9.5
(1,1,0)	2.05	(1.40-3.02)	1.59	(0.90-2.81)	2.4	1.8
<i>Fluctuation</i>						
(1,0,1)	1.45	(1.02-2.07)	1.36	(0.85-2.18)	3.8	3.9
(0,1,0)	1.97	(1.49-2.60)	1.12	(0.54-2.32)	3.0	1.0

Note: Ages 50-74 at baseline. (0,0,0) is age-25 BMI<25, middle age BMI<30, and baseline BMI<30. Models adjust for baseline age, sex, race/ethnicity, educational attainment and baseline cigarette smoking (current, former, never).

^aReference category.

Table 3
Binary Models Nested within Saturated Binary Model Predicting Death from Any Cause

Model	Variable	NHANES			NHEFS		
		HR	(95% CI)	F-test ^a	HR	(95% CI)	F-test ^a
Additive	O1	1.26	(1.09-1.46)		1.50	(1.19-1.90)	
	O2	1.24	(1.00-1.55)	P=0.011	1.25	(0.93-1.68)	P=0.908
	O3	1.09	(0.85-1.41)		1.04	(0.81-1.34)	
Duration ^b	(O1+O2+O3)	1.19	(1.12-1.27)	P=0.000	1.26	(1.14-1.39)	P=0.582
	O1	1.71	(1.43-2.06)		1.96	(1.44-2.65)	
Weight Change	O2-O1	1.36	(1.12-1.65)	P=0.011	1.30	(0.92-1.85)	P=0.908
	O3-O2	1.09	(0.85-1.41)		1.04	(0.81-1.34)	

Notes: Ages 50-74 at baseline. O1 indicates a BMI 25 at age 25 years. O2 and O3 indicate a BMI 30 at middle age and baseline, respectively. Models adjust for baseline age, sex, race/ethnicity, educational attainment and baseline cigarette smoking (current, former, never).

^a P-values for F-test comparing current model with fully saturated binary model in Table 2.

^b P-values for F-test comparing duration model with additive model are 0.654 (NHANES) and 0.183 (NHEFS).

Table 4
Fully Interactive Continuous Model Predicting Death from Any Cause

<i>Variable</i>	NHANES		NHEFS	
	<i>HR</i>	<i>(95% CI)</i>	<i>HR</i>	<i>(95% CI)</i>
BMI1	1.074	(1.003-1.150)	1.286	(1.070-1.546)
BMI2	1.059	(1.027-1.092)	1.127	(1.017-1.250)
BMI3	1.045	(1.004-1.088)	1.002	(0.940-1.068)
BMI1*BMI2	0.994	(0.985-1.004)	0.979	(0.955-1.005)
BMI1*BMI3	1.002	(0.990-1.013)	0.989	(0.965-1.013)
BMI2*BMI3	0.995	(0.991-1.000)	0.999	(0.984-1.013)
BMI1*BMI2*BMI3	1.000	(0.999-1.001)	1.001	(0.999-1.003)

Note: Ages 50-74 at baseline. BMI coded 0 for BMI ≥ 30.0 and BMI <30.0 otherwise. Models adjust for baseline age, sex, race/ethnicity, educational attainment and baseline cigarette smoking (current, former, never).

Table 5
Continuous Models Predicting Death from Any Cause

Model	Variable	NHANES			NHEFS		
		HR	(95% CI)	F-test ^a	HR	(95% CI)	F-test ^d
Additive	BMI1	1.025	(0.975-1.078)		1.047	(0.960-1.141)	
	BMI2	1.028	(1.005-1.052)	P=0.237	1.087	(1.030-1.147)	P=0.170
	BMI3	1.026	(0.994-1.060)		1.001	(0.934-1.073)	
Duration ^b	(BMI1+BMI2+BMI3)	1.027	(1.017-1.037)	P=0.310	1.043	(1.020-1.067)	P=0.233
Weight Change	BM 11	1.082	(1.040-1.125)		1.139	(1.065-1.219)	
	(BMI2-BMI1)	1.055	(1.027-1.085)	P=0.237	1.088	(1.007-1.177)	P=0.170
	(BMI3-BMI2)	1.026	(0.994-1.060)		1.001	(0.934-1.073)	
Weight Change ^c (differentiated)	BM 11	1.038	(0.987-1.092)		1.045	(0.934-1.168)	
	Loss (2-1)	1.029	(0.936-1.131)		1.172	(1.005-1.368)	
	Gain (2-1)	1.028	(0.993-1.065)	n/a	1.044	(0.926-1.177)	n/a
	Loss (3-2)	1.034	(0.986-1.084)		1.101	(0.948-1.280)	
	Gain (3-2)	1.053	(1.013-1.095)		1.019	(0.952-1.091)	

Note: Ages 50-74 at baseline. BMI coded 0 for BMI <30.0 and BMI ≥30.0 otherwise. Models adjust for baseline age, sex, race/ethnicity, educational attainment and baseline cigarette smoking (current, former, never).

^a P-values for F-test comparing current model with fully interactive model in Table 4.

^b P-values for F-test comparing duration model with additive model are 0.995 (NHANES) and 0.233 (NHEFS).

^c Model not nested in fully interactive model shown in Table 4.

Table 6
Alternative Duration Models Predicting Death from Any Cause

Model	NHANES			NHEFS		
	HR	(95% CI)	Coefficient/SE	HR	(95% CI)	Coefficient/SE
Obesity Duration (years)	1.016	(1.010-1.022)	5.298	1.015	(1.006-1.023)	3.331
Obesity Duration (percent)	1.007	(1.004-1.009)	5.350	1.006	(1.003-1.010)	3.705
Yrs. Since Becoming Obese	1.015	(1.098-1.021)	5.617	1.012	(1.005-1.020)	3.464
BMI-years above 30.0	1.002	(1.001-1.003)	5.260	1.003	(1.001-1.005)	3.434

Note: Ages 50-74 at baseline. Models adjust for baseline age, sex, race/ethnicity, educational attainment, and cigarette smoking (current, former, never).