Estimating the Effects of Weight and Weight Change Using a Dynamic Causal Model

Bochen Cao, University of Pennsylvania

Neil Mehta, Ph.D., Emory University

Introduction

An abundant number of studies aim to investigate the association between high body weight and mortality (1–9). A well-known challenge in estimating the mortality risks of high body weight is accounting for reverse causality attributable to illness-associated weight loss. Reverse causality is thought to downwardly bias the observed mortality risks of high body weight. Given that the likelihood of chronic and acute illnesses rises with age, reverse causality is most threatening to estimates derived from elderly populations. Similarly, many smoking-related illnesses are known to be associated with disease-induced weight loss and estimates among smokers are also thought to be highly influenced by reverse causal processes. These disease include chronic obstructive pulmonary disease (COPD), many cancers, cardiac diseases, and renal disease (10–14). To date, most attempts to deal with reverse causality are thought to be inadequate (15).

Treatment of diseases that cause weight loss are best thought of as time-varying confounders to the body weight and mortality association because they fulfill three criteria: (1) body weight predicts the onset of disease, (2) disease predicts subsequent body weight; and (3) diseases are themselves independently predictive of mortality (16,17).

This analysis attempts to address the time-varying confounding of the body weight and mortality association by using a dynamic marginal structural model (MSM) (16–18). We use the nationally representative Health and Retirement Study (HRS). We compare estimates from conventional survival techniques to MSMs and assess the magnitude of bias that may be caused by not fully accounting for time-varying processes. We specifically fill the gaps in existing literature by: (1) modeling both baseline weight and time-varying weight change using multiple waves of the HRS, and (2) treating both incident illness and health behaviors as time-varying confounders. To our knowledge, no prior study has used a marginal structural model to provide less biased estimates of the mortality risks of body weight and body weight change.

Data

Data for this study is drawn from the HRS. The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. It is a longitudinal survey of Americans aged 50 and above(19). This study is based on two of five

cohorts who entered the survey at approximately the same ages: the initial HRS cohort that was born in 1931-1941 and entered survey in 1992 and the War Babies (WB) cohort that born in 1942-1947 and entered survey in 1998.

The initial HRS cohort and the WB cohort have a sample size of 9,763 and 2,760, respectively, providing a total of 12,523 respondents. In order to calculate weight change between subsequent interviews, we exclude those who died or dropped out of the study before the second interview, and those whose body mass index (BMI) is missing in any interview. We further excluded those with very high baseline BMI (>60) and those have experienced extraordinary weight loss (>30% of body weight) between two interviews. This leads to a sample of 8,678 respondents and 67,772 observations (person-interviews). Analyses in this study are performed with the RAND HRS data, version L (20).

Methods

We modeled two indicators of BMI: a static measure (BMI at baseline) and a dynamic measure (BMI change between waves). All models adjust for socio-demographic variables (sex, age at baseline, race/ethnicity, education, marital status and household income) and health behaviors (smoking status and frequency of vigorous physical activity per week). We compared estimates from three sets of models. Model 1 is a conventional Cox model in which baseline weight status and weight change between wave 1 and wave 2 was used. All other covariates (socio-demographic and health behaviors) were treated as fixed baseline characteristics. Model 2 is a Cox model that incorporates information from all waves of data treating all dynamic covariates as time-varying. Model 3 includes an identical set of variables as Model 2, but is estimated using an MSM to account for the time-varying confounding. The MSM creates a pseudo-population in which the association between BMI change and mortality is not confounded(16,17). This pseudo-population is created by re-weighting the data from observational longitudinal study based on observed covariates. A single weight is generated for each person-interview in this process. The newly created weights are then supplied to pooled logistic regression. We estimated all models with and without health conditions. The health conditions assessed include an indicator variable for diagnosis of one of five chronic diseases (diabetes, cancer, lung disease, heart problem and stroke) and a separate variable for self-rated health status (good/ poor).

Preliminary Results

Table 1 presents the baseline characteristics overall and by body weight change over time during the entire study. Overall, about 20% of the participants died during follow-up. Overweight people constitutes the largest group (25<=BMI<30; 41.31%) of the sample, followed by those with normal weight (18.5<=BMI<25; 33.58%). Class II/III obese (BMI>=35; 7.01%) and underweight (BMI<18.5; 1.14%) are observed in only a small proportion of the sample. Table 1 shows that relative to those who remained stable weight throughout the study, every type of weight change is associated with more current/former smokers, less vigorous physical activity,

worse self-rated health, and more diagnoses of chronic disease both prior to and during the study. Those who failed to remain stable weight are also more prone to be overweight and obese at baseline, among which those experienced large weight loss have the largest fraction of being obese (35.55%) which is more than double of the proportion obese among those remained stable weight (15.7%).

Table 2 presents the hazard ratios across the three sets of models (Models 1-3). The left side of the table shows models that excluded the health conditions (Panel A) and the right side of the Table shows results for models that included the health conditions (Panel B). Estimates for all other predictors are omitted from the Table. Normal weight (18.5<=BMI<25) at baseline and stable weight change (-5% to 5% of previous weight) are used as reference categories.

Results in Table 2 indicate a U-shaped association for both initial weight and weight change for all models. A comparison of Model 1 with Model 2 (in both Panels A and B) generally shows a substantial increase in the risk of weight change. The HRs for baseline weight, on the other hand, generally decreased and is most evident for class II/III obesity. These findings indicate that fluctuations in weight are more highly predictive of short-term mortality compared to longer term mortality and that a portion of the effect of baseline weight and mortality is explained by subsequent changes in weight. Comparing Model 2 to the MSM (Model 3) we observe smaller changes compared to moving from Model 1 to Model 2. However, the comparison of Model 2 to Model 3 (in both Panels) highlights that failure to fully adjust for confounding effects along the causal pathway will likely yield underestimated effects of baseline weight.

One additional comparison is noteworthy to highlight: Model 3 in Panel A (without health conditions) with Model 3 in Panel B (with health conditions). The inclusion of the health conditions results in smaller effects for weight loss and being underweight. This is expected because individuals with diagnosed preexisting diseases and other subclinical diseases are inclined to lose weight and be leaner, as well as have increased risk of mortality. The effects of weight gain and obesity also decline. This decline is likely due to disease's role as an intermediary on the causal pathway between obesity and mortality.

Discussion and Future Direction

Our results suggest that both initial weight and subsequent weight are predictive of mortality and have a U-shaped association. Being underweight and class II/III obese would raise mortality risk by 120% and 40% respectively relatively to people in normal weight, while being overweight and class I obese at baseline are not associated with excess mortality. All types of weight change, except for small weight gain, lead to increased mortality, relative to stable weight change within -5% to 5% of initial body weight. On the one hand, large weight loss will lead to a mortality risk that is four times higher than staying in the stable weight range, and small weight loss is about 1.8 times riskier. On the other hand, large weight gain is associated with mortality risks that are

1.7 times higher. Our results suggest that the larger hazard ratios may indicate weight change has stronger effects on mortality than initial weight status. The next step in this analysis is applying these models to samples stratified by smoking status. We expect the effect of time-varying confounding by health behaviors to be stronger among ever smokers compared to never smokers.

Table 1: Baseline Characteristics by Weight Change Status Through All Interviews

	Whole Sample (n=8,678)	Large Weight Loss At Least Once (n=2,337)	Small Weight Loss At Least Once (n=4,314)	Stable Weight All Time (n=1,414)	Small Weight Gain At Least Once (n=5,062)	Large Weight Gain At Least Once (n=2,610)
Women	50.97	59.22	53.76	41.02	53.38	60.88
Mean age at first interview, Years	55.14 (3.17)	55.33(3.21)	55.20(3.19)	55.26(3.16)	55.01(3.15)	54.93(3.14)
Total percent dying	20.29	27.00	18.57	22.91	15.73	18.74
Mean number of follow-up years						
For those who died	10.56(4.69)	11.90(4.39)	12.21(4.18)	7.33(4.11)	12.42(4.17)	12.37(4.22)
For those who were censored	14.80(4.93)	16.08(3.80)	16.09(3.69)	11.15(6.42)	15.93(3.75)	16.03(3.68)
Race/Ethnicity						
White, non-Hispanic	75.43	71.16	73.67	79	75.86	72.26
Black, non-Hispanic	15.08	18.4	16.32	12.66	14.54	16.86
Hispanic	7.37	8.69	8.14	6.01	7.55	9
Other	2.11	1.75	1.88	2.33	2.05	1.88
Education						
Less than a high school diploma	22.31	28.07	23.83	18.03	22	25.82
High school diploma/GED	37.48	37.44	37.26	36.56	37.29	38.97
Some college	20.18	18.53	20.59	19.09	20.77	19.92
College degree or higher	20.02	15.96	18.32	26.31	19.94	15.29
Marital Status						
Married	74.91	71.39	73.84	78.58	75.23	71.3
Never married	4	3.95	4.05	3.62	3.9	4.19
Divorced/separated	15.11	17.44	15.37	13.33	14.86	17.43
Widowed	5.98	7.22	6.74	4.47	6	7.08
Mean Household Income, $1,000s	54.10(62.14)	43.98(48.26)	51.69(79.48)	64.86(80.63)	53.68(92.26)	49.30(90.61)
Smoking Status						
Never smoker	36.81	34.83	36.95	36.85	37.71	35.59
Former smoker	36.66	34.02	35.95	39.46	36.78	33.95
Current smoker	26.54	31.15	27.1	23.69	25.5	30.46
Vigorous Physical Activity (≥3 times per week)	25.55	22.04	24.4	29.21	25.04	24.75

Notes: Numbers are percentages unless otherwise noted. Standard deviations for continuous variables are in parentheses.

Table 1 (Continued): Baseline Characteristics by Weight Change Status Through All Interviews

	Whole Sample (n=8,678)	**Large Weight Loss At Least Once (n=2,337)**	**Small Weight Loss At Least Once (n=4,314)**	**Stable Weight All Time (n=1,414)**	**Small Weight Gain At Least Once (n=5,062)**	**Large Weight Gain At Least Once (n=2,610)**
Baseline BMI Categories						
Underweight (<18.5)	1.14	0.73	1	1.49	0.97	1.38
Normal (18.5–24.9)	33.58	24.99	29.25	44.34	32	28.43
Overweight (25.0–29.9)	41.31	38.72	43.23	38.47	42.67	40.11
Class I obese (30–34.9)	16.96	23.06	18.94	11.74	17.4	20.73
Class II/III obese (≥35.0)	7.01	12.49	7.58	3.96	6.95	9.35
Self-report of health						
Excellent	23.04	16.26	22.28	27.09	23.55	19.12
Very Good	29.43	26.27	28.44	31.61	29.53	27.24
Good	27.24	29.44	28.23	24.54	27.99	29.31
Fair	13.26	17.63	14.28	10.25	13.14	16.05
Poor	7.03	10.4	6.77	6.51	5.79	8.28
Chronic Diseases diagnosed before entering the study						
Diabetes	10.46	14.08	10.67	9.62	8.75	11
Cancer	5.19	6.5	5.49	4.46	5.16	5.86
Lung Disease	7.14	9.07	7.23	5.73	6.72	8.31
Heart Problem	12.18	13.99	12.12	11.6	11.75	12.18
Stroke	2.57	3.63	2.41	2.12	2.21	2.95
No preexisting diseases	70.81	65	70.12	74.05	72.36	68.54
Chronic Diseases diagnosed during the study						
Diabetes	26.17	34.27	29.53	17.11	27.01	30.92
Cancer	19.59	23.75	21.44	13.72	19.93	21.03
Lung Disease	15.61	21.01	17.08	10.4	15.74	19.89
Heart Problem	31.55	40.39	35.4	22.14	32.67	36.59
Stroke	10.43	16.35	12.22	5.3	10.9	13.6
No preexisting diseases	35.92	24.48	30.2	50.57	34.16	29.23

Notes: Numbers are percentages unless otherwise noted. Standard deviations for continuous variables are in parentheses.

Table 2: Adjusted Effects of Baseline BMI and Weight Change Over Time on Mortality

Parameter	Panel A (without health conditions)			Panel B (with health conditions)		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Weight Loss 10%+	1.985 *** (1.689,2.332)	3.821 *** (3.288,4.44)	4.268 *** (3.662,4.973)	1.842 *** (1.568,2.165)	3.557 *** (3.053,4.145)	3.982 *** (3.408,4.653)
Weight Loss 5-10%	1.475 *** (1.289,1.687)	1.78 *** (1.544,2.053)	1.926 *** (1.666,2.227)	1.421 *** (1.242,1.626)	1.719 *** (1.489,1.985)	1.845 *** (1.593,2.136)
Weight Gain 5-10%	1.047 . (0.911,1.202)	1.118 . (0.953,1.311)	1.184 * (1.007,1.391)	1.009 . (0.879,1.159)	1.105 . (0.941,1.297)	1.172 . (0.997,1.378)
Weight Gain 10%+	1.185 . (0.987,1.421)	1.649 *** (1.368,1.988)	1.76 *** (1.454,2.131)	1.125 . (0.937,1.35)	1.563 *** (1.295,1.887)	1.659 *** (1.368,2.012)
Underweight	2.241 *** (1.614,3.11)	2.138 *** (1.491,3.067)	2.372 *** (1.571,3.583)	1.988 *** (1.432,2.76)	1.975 *** (1.359,2.871)	2.172 *** (1.461,3.23)
Overweight	0.964 . (0.864,1.075)	0.878 * (0.78,0.988)	0.941 . (0.834,1.061)	0.943 . (0.834,1.061)	0.878 * (0.779,0.989)	0.921 . (0.815,1.041)
Obese I	1.1 . (0.961,1.259)	0.921 . (0.797,1.064)	1.046 . (0.902,1.213)	0.972 . (0.849,1.113)	0.889 . (0.768,1.029)	0.95 . (0.818,1.104)
Obese II/III	1.763 *** (1.502,2.069)	1.287 ** (1.079,1.536)	1.722 *** (1.437,2.064)	1.412 *** (1.202,1.66)	1.18 . (0.985,1.414)	1.391 *** (1.156,1.674)

Notes:

Models 1: Conventional Cox proportional hazard model is used. Weight change variables refer only change in the period between baseline and the next interview following baseline. Weight status and all other covariates refer only to baseline measures.

Models 2: Cox model with time-dependent covariates is used. Weight status and the time-independent covariates refer only to baseline measures. Weight change variable and all other covariates are time-varying.

Models 3: Marginal Structural Model is used. Weight status and the time-independent covariates refer only to baseline measures. Weight change variable and all other covariates are time-varying.

Panel A: Covariates include SES and socio-demographic variables (gender, age at first interview, race/ethnicity, education, marital status and household income), and variables for health behaviors (smoking status and frequency of vigorous physical work per-week).

Panel B: Variables for health conditions (previous diagnosis of chronic diseases and self-rated health conditions) are also included.

References

1. Comoni-Huntley J, Harris T, Everett D. An overview of body weight of older persons, including the impact on mortality. *J Clin Epidemiol*. 1991;44(8).

2. Tayback M, Kumanyika S, Chee E. Body weight as a risk factor in the elderly. *Archives of internal medicine*. 1990;150(5):1065–72.

3. Manson JE, Stampfer MJ, Hennekens CH, et al. Body weight and longevity. A reassessment. *JAMA : the journal of the American Medical Association*. 1987;257(3):353–8.

4. Allison DB, Faith MS, Heo M, et al. Hypothesis concerning the U-shaped relation between body mass index and mortality. *American journal of epidemiology*. 1997;146(4):339–49.

5. Singh PN, Lindsted KD. Body mass and 26-year risk of mortality from specific diseases among women who never smoked. *Epidemiology (Cambridge, Mass.)*. 1998;9(3):246–54.

6. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *The New England journal of medicine*. 2010;363(23):2211–9.

7. Flegal KM, Kit BK, Orpana H. Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories. 2013;309(1):71–82.

8. Gelber RP, Kurth T, Manson JE, et al. Body mass index and mortality in men: evaluating the shape of the association. *International journal of obesity (2005)*. 2007;31(8):1240–7.

9. Adams K, Schatzkin A. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. ... *England Journal of* .... 2006;:763–778.

10. Preston SH, Mehta NK, Stokes A. Modeling obesity histories in cohort analyses of health and mortality. *Epidemiology (Cambridge, Mass.)*. 2013;24(1):158–66.

11. Claessen H, Brenner H, Drath C, et al. Repeated measures of body mass index and risk of health related outcomes. *European journal of epidemiology*. 2012;27(3):215–24.

12. Reas DL, Nygård JF, Svensson E, et al. Changes in body mass index by age, gender, and socio-economic status among a cohort of Norwegian men and women (1990-2001). *BMC public health*. 2007;7:269.

13. He J, McGee D, Niu X, et al. Examining the dynamic association of BMI and mortality in the Framingham Heart Study. *International journal of environmental research and public health*. 2009;6(12):3115–26.

14. He J. Modeling the dynamic association of BMI and mortality in the Framingham Heart Study. *Annals of epidemiology*. 2011;21(7):517–25.

15. Mehta N and VC. Obesity and Mortality. In: Cawley J, ed. *Handbook of the Social Science of Obesity*. Oxford University Press; 2011

16. Hernán M a, Robins JM. Estimating causal effects from epidemiological data. *Journal of epidemiology and community health*. 2006;60(7):578–86.

17. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550–560.

18. JM R. Marginal structural models. *In: 1997 Proceedings of the Section on Bayesian Statistical Science, Alexandria, VA: American Statistical Association*. 1998;:1–10.

19. Health and Retirement Study, public use dataset. *Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI*. 2010;

20. RAND. RAND HRS Data, Version L. *RAND Center for the Study of Aging [producer] with funding from the National Institute on Aging and the Social Security Administration, Santa Monica, CA*. 2011;

21. Manson JE, Bassuk SS, Hu FB, et al. Estimating the number of deaths due to obesity: can the divergent findings be reconciled? *Journal of women's health (2002)*. 2007;16(2):168–76.

22. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *The New England journal of medicine*. 1999;341(15):1097–105.